FDA BRIEFING DOCUMENT

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

JANUARY 22, 2015

NDA 207-501: Cresemba® (Isavuconazonium) for Injection

NDA 207-500: Cresemba® (Isavuconazonium) Capsules

APPLICANT: Astellas Pharma US, Inc.

PROPOSED INDICATIONS:

Invasive Aspergillosis and Invasive Mucormycosis

DISCLAIMER STATEMENT

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1 INTRODUCTION

Astellas Pharma US submitted two new drug applications (NDAs) on July 8, 2014, for isavuconazonium (BAL8557-002, ASP9766) for the treatment of invasive aspergillosis and treatment of invasive mucormycosis in patients 18 years of age and older.

This briefing document contains a summary of the contents of the NDAs and a discussion of the efficacy and safety data for isavuconazonium in the treatment of invasive aspergillosis and invasive mucormycosis.

Invasive aspergillosis is an important cause of mortality and morbidity in patients with prolonged neutropenia, hematologic malignancies, and allogeneic hematopoietic stem cell transplantation (HSCT) recipients.[1] Invasive mucormycosis is relatively uncommon and occurs in patients with severe immunocompromise, hyperglycemia, iron overload, and occasionally in healthy patients with traumatic injuries. Invasive mucormycosis is one of the most life-threatening mold infections in patients with hematologic malignancies and in HSCT recipients[2,3,4]. In a prospective surveillance study for invasive fungal infections (IFIs) in HSCT recipients, among 983 invasive fungal infections in 875 HSCT recipients, invasive aspergillosis (43%), invasive candidiasis (28%), and mucormycosis (8%) were the most common IFIs.[5] Current FDA-approved therapies for treatment of invasive aspergillosis include amphotericin formulations, itraconazole, voriconazole, and caspofungin. Amphotericin B is approved for the treatment of invasive mucormycosis.

The efficacy and safety data for the two indications are primarily supported by the results from a global, multicenter, randomized, controlled phase 3 trial of isavuconazonium compared to voriconazole for the treatment of invasive aspergillosis and results from an open-label, multicenter, single-arm study of isavuconazonium for the treatment of invasive mucormycosis, and other rare molds, yeasts, or dimorphic fungi.

[1] Walsh, T.J., Anaissie, E.J., Denning, D.W., *et al.* Treatment of Aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008; 46:327- 60.
[2] Roden, M.M., Zaoutis, T.E., Buchanan, W.L., *et al.* "Epidemiology and outcome of zygomycosis: a review of 929 reported cases." Clin Infect Dis. 2005; 41:634-53.
[3] Skiada A., Pagano L., Groll A., *et al*. "Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007." Clin Microbiol Infect. 2011 Dec; 17(12):1859-67.
[4] Chamilos, G., Lewis, R.E., Kontoyiannis, D.P. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." Clin Infect Dis. 2008 Aug 15; 47(4):503-9.
[5] Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50:1091–1100.

2 ISAVUCONAZONIUM PRODUCT INFORMATION

Isavuconazonium is a prodrug of isavuconazole, a triazole antifungal drug.

Isavuconazonium is available as a hard capsule for oral administration and a sterile, lyophilized powder for intravenous infusion after reconstitution. Following reconstitution, the intravenous isavuconazonium formulation may spontaneously hydrolyze in aqueous solution and precipitate as insoluble isavuconazole. As a result, the study drug was administered through an inline filter to remove particulates.

Following intravenous administration, isavuconazonium is hydrolyzed to the active moiety isavuconazole (BAL4815) and an inactive cleavage product (BAL8728). After oral administration, the drug is cleaved in the gastrointestinal tract by hydrolysis and isavuconazole is absorbed. Treatment consists of a loading dose of 200 mg every eight hours for the first 48 hours via oral or intravenous administration. The maintenance dose is 200 mg per day via oral or intravenous administration.

3 ISAVUCONAZONIUM CLINICAL DEVELOPMENT AND REGULATORY HISTORY

The clinical development program evaluated 1692 subjects exposed to isavuconazonium, including 1145 subjects in 40 phase 1 studies, 144 subjects in two phase 2 trials and 403 subjects in two phase 3 trials. A tabular summary of the phase 2 and 3 clinical trials with isavuconazonium is provided in section 7.

Isavuconazonium was designated as a Qualified Infectious Disease Product (QIDP) for the indications of treatment of invasive aspergillosis in November 2013 and treatment of invasive mucormycosis in February 2014. Orphan drug designation was granted for the treatment of invasive aspergillosis in May 2013 and for the treatment of mucormycosis in October 2013.

4 CLINICAL PHARMACOLOGY

Summary of Pharmacokinetics

Isavuconazonium is a prodrug that is rapidly hydrolyzed in blood to the active moiety, isavuconazole, by esterases, predominately butyrylcholinesterase. Following IV administration, concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly following the end of administration. The prodrug was below the level of detection by 1.25 hours after the start of a 1 hour infusion. The total exposure of the prodrug based on AUC was less than 1% that of isavuconazole. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion.

Studies in healthy subjects demonstrated that the systemic exposure to isavuconazole is dose proportional following oral or IV doses up to 600 mg per day.

Absorption

The absolute bioavailability of isavuconazole from the oral capsule was approximately 98%. Following oral administration of isavuconazonium, the maximum concentrations of isavuconazole in the systemic circulation are reached in approximately two to three hours. Concurrent administration of isavuconazonium capsules with a high-fat breakfast had no clinically relevant effect on the bioavailability and pharmacokinetics of isavuconazole.

Distribution

Isavuconazole is extensively distributed with a mean volume of distribution at steady-state of approximately 450 L. Isavuconazole is extensively bound (> 99%) to plasma proteins *in vitro*.

Following a single oral dose of [cyano-^{14}C]-labeled isavuconazonium, mean blood-to-plasma concentration ratios of radioactivity ranged from 0.482 to 0.665 through 264 hours postdose, indicating minimal sequestration of radioactivity within red blood cells. Similar blood-to-plasma concentration ratios were obtained following a single IV dose of [pyridinylmethyl-^{14}C]-labeled isavuconazonium.

Metabolism

The *in vitro* metabolism of isavuconazole was investigated in human hepatocytes and liver microsomes. Isavuconazole is a substrate of CYP3A4 and CYP3A5 and is metabolized to a small extent to oxidative metabolites that are further conjugated. *In vitro*, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The drug is an inhibitor of P-gp, BCRP and OCT2-mediated drug transporters. *In vitro*, isavuconazole is also a weak inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9.

Excretion

Following IV administration of [pyridinylmethyl-^{14}C] isavuconazonium, 95% of the total radioactive dose was excreted in the urine; the major form of urine radioactivity was the oxidative carbamate cleavage metabolite M4 (56% of total dose). Renal elimination of intact cleavage product was less than 1% of the total dose administered. Based on a population PK analysis of healthy subjects and patients, the mean half-life of isavuconazole in plasma was 130 hours.

Intrinsic Factors

Based on population PK analysis, race (Asian/non-Asian) was a significant covariate on clearance and BMI was a significant covariate on volume of distribution of isavuconazole. None of the covariates of age, gender, weight or race require dose adjustment based on exposure since the overall exposure-response (E-R) relationship for efficacy and safety was flat within the concentration range achieved in the Phase 3 trial, 9766-CL-0104.

The AUC of isavuconazole following a single oral dose of 200 mg in elderly subjects (≥ 65 years) was similar to that in younger subjects (18 to 45 years). The AUC was similar between younger female and male subjects and between elderly and younger males. AUC values in elderly females were 38% and 47% greater than AUC estimates obtained in males and younger females, respectively. The PK differences in elderly females receiving isavuconazonium are not considered to be clinically significant. Therefore, no dose adjustment is required based on age and gender.

Isavuconazole AUC and C_{max} were not affected to a clinically meaningful extent in subjects with mild, moderate and severe renal impairment relative to healthy controls. No dose adjustment is necessary in patients with renal impairment. Isavuconazole is not readily dialyzable. A dose adjustment is not warranted in patients with ESRD.

After a single 100 mg (Oral and IV) dose of isavuconazonium was administered to 32 patients with mild (Child-Pugh Class A) hepatic impairment and 32 patients with moderate (Child-Pugh Class B) hepatic impairment, the total isavuconazole exposure (AUC_{last}) increased 27% to 42% in the Child-Pugh Class A group and 11% to 69% in Child-Pugh Class B group, respectively, relative to 32 age and weight-matched healthy subjects with normal hepatic function. No dosage adjustment of isavuconazonium is recommended in patients with mild to moderate hepatic disease. Isavuconazonium has not been studied in patients with severe hepatic disease (Child-Pugh Class C) and therefore administration is not recommended in these patients.

Extrinsic Factors

The effects of extrinsic factors such as herbal products, smoking and alcohol use have not been studied. *In vitro* metabolism, inhibition/induction, and transporter experiments suggest the potential for *in vivo* drug interactions. The *in vivo* drug interaction potential of isavuconazonium has been evaluated in several Phase 1 drug interaction studies in healthy volunteers.

Isavuconazole is a sensitive CYP3A4 substrate and use of isavuconazonium with strong CYP3A4 inhibitors and inducers is not recommended. Upon co-administration, ketoconazole increased the isavuconazole C_{max} by 9% and isavuconazole AUC by 422% after multiple dose administration of ketoconazole (200 mg twice daily) for 24 days and a single oral dose of isavuconazonium equivalent to 200 mg of isavuconazole. The combination of lopinavir/ritonavir (400 mg/100 mg twice daily) increased the C_{max} and AUC of isavuconazole following administration of the clinical oral dose of isavuconazonium by 74% and 96%, respectively, while isavuconazole decreased the mean AUC of lopinavir and ritonavir by 27% and 31%, respectively. Rifampin when given at a dosage regimen of 600 mg QD for 7 days reduced the mean C_{max} and AUC_{inf} of isavuconazole following a single oral clinical dose of isavuconazonium by 75% and 97 %, respectively.

Multiple oral doses of isavuconazonium increased the C_{max} and AUC of midazolam by 72% and103%, respectively. Multiple oral doses of isavuconazonium also increased the C_{max} and AUC of sirolimus by 65% and 84%, respectively, and increased the C_{max} and AUC of tacrolimus by 42% and 125%, respectively. The use of routine therapeutic drug concentration monitoring (TDM) of tacrolimus, sirolimus, and cyclosporine should enable concomitant administration with isavuconazonium.

Thorough QT (TQT) Trial:

The QT Interdisciplinary Review Team at FDA concluded the following based on a review of the TQT trial conducted by the sponsor:

At an oral isavuconazonium capsule dose three times the recommended therapeutic maintenance dose, isavuconazole did not prolong the QT interval to any clinically relevant extent. A dose- and concentration-related shortening of the QTc interval was observed with isavuconazole, probably due to a slight block of the calcium channel. The clinical significance of the drug-induced reduced QT interval is discussed in Section 9.7.3 of this briefing document.

5 MICROBIOLOGY

Mechanism of Action

The mechanism of action of isavuconazole is similar to other antifungal azoles and involves the inhibition of cytochrome P450 sterol 14 α-demethylase ($P450_{14DM}$) enzyme, which has a role in the synthesis of ergosterol, a component of the cell membrane (encoded by the genes *cyp51A* and *cyp51B*) present in all fungi. Depletion of ergosterol disrupts the structure and function of the fungal cell membrane. There is an accumulation of toxic methylated sterol precursors, leading to inhibition of fungal growth. Isavuconazole inhibits $P450_{14DM}$ enzyme activity in *Candida albicans* at about a 100 fold lower concentration than that of mammalian rat liver cells.

In Vitro Activity

The isavuconazole *in vitro* susceptibility testing was standardized using a panel of quality control (QC) strains recommended by Clinical Laboratory Standards Institute (CLSI). The QC strains selected (to confirm that antifungal agents are present at correct concentrations and to monitor antifungal stability) were appropriate. Based on the intra- and inter-laboratory standardization of the *in vitro* susceptibility testing of isavuconazole, the QC strains and the minimum inhibitory concentration (MIC) range selected for *in vitro* susceptibility testing against filamentous fungi by the CLSI method were appropriate and are as follows:

- *Paecilomyces variotii* MYA 3630 at a range of 0.06 – 0.5 μg/ml, and
- *Aspergillus flavus* ATCC 204304 at a range of 0.5 – 4 μg/ml.

The activity of isavuconazole was measured *in vitro* against the different species of *Aspergillus* and Mucorales. There were three main sources of information for evaluating the *in vitro* activity of isavuconazole:

- Surveillance studies.
- Database of published and unpublished studies compiled by the applicant.
- Isolates collected from clinical trials.

Among the *Aspergillus* species, the isavuconazole MIC_{90} values were lower against *Aspergillus fumigatus, Aspergillus flavus, Aspergillus nidulans,* and *Aspergillus terreus* compared to

Aspergillus niger (Table 1). There did not appear to be any effect of geographic region on the results. Isavuconazole MIC_{90} values were similar to those of itraconazole and voriconazole. Posaconazole was approximately four-fold more active. The MIC_{90} values of echinocandins were low with the exception of caspofungin.

Table 1: Summary of *in vitro* activity of isavuconazole against *Aspergillus* and Mucorales species (CLSI method)

Species	MIC_{90} µg/mL (n)					
	Surveillance study		Database**	Other published studies	Clinical trial isolates	Espinel-Ingroff *et al.* (2013)/ CLSI ECV[1]
	2011	2012				
***Aspergillus* species**						
A. flavus	1 (10)	2 (11)	4 (145)		2 (23)	1 (444) / 1
A. fumigatus	1 (71)	2 (90)	1 (875)	0.39 (12)	1 (54)	1 (855) / 1
A. nidulans	-	-	1 (85)	1 (63)	-	1 (106) / -
A. niger	4 (11)	4 (11)	2 (101)	1.56 (1)*	8 (11)	2 (207) / 4
A. oryzae	-	-	-	0.39 (1)*	-	-
A. terreus	-	-	1 (432)	0.125 - 1(135)*	0.25-2 (8)*	0.5 (384) / 1
A. lentulus	-	-	-	0.25 (15)	-	-
A. westerdijkiae	-	-	-	-	2 (1)	-
Other *Aspergillus* species	2 (12)[!]	2 (18)[!]	-	-	-	-
***Aspergillus* species**	**2 (104)**	**2 (130)**	**2 (1717)**	**0.125 – 2 (227)***	**2 (96)**	**-**
Mucorales						
***Lichthelmia (Absidia)* species (Total)**[!]	-	-	**8 (67)**	-	-	-
L. corymbifera	-	-	8 (44)	8 (17)	8-16 (4)*	-
Lichthelmia species NOS	-	-	32 (23)	-	-	-
Cunninghamella species (Total)[!]	-	-	32 (13)	-	-	-
***Mucor* species (Total)**[!]	-	-	**16 (68)**	-	-	-
M. circinelloides	-	>8 (1)*	8 (18)	8 (16)	32 (1)*	-
Rhizomucor species (All)[!]	-	-	-	2 - >8 (9)*	-	-
R. pusillus	4 (1)*	-	-	-	8-32 (3)*	-
***Rhizopus* species (Total)**[!]	-	-	**8 (134)**	-	-	-
R. arrhizus	-	-	4 (28)	4 (27)	-	-
R. microsporus	1-2 (2)*	1-4 (2)*	2 (41)	-	16 (1)*	-
R. oryzae	-	>8 (1)*	4 (11)	-	0.5 - 32 (9)	-
R. azygosporus	-	-	-	-	1 (1)*	-
Rhizopus species NOS	-	-	16 (52)	-	32 (11)	-
Apophysomyces elegans	-	-	-	4 (18)	-	-
Actinomucor elegans	-	-	-	-	0.25 (1)	-

* represent range. If number of isolates less than 10, MIC_{90} value was not calculated or not available.
**Database results include surveillance study results of 2011.
[!]Include *A. terreus, A. nidulans, A. foetidus, and A. sydowii*.
NOS=Not otherwise specified
[1]Epidemiological cut-off values (ECVs) based on a study by Espinel-Ingroff *et al*. (2013); ECVs approved by the CLSI.

The MICs were higher against the hyphae compared to conidia of *Aspergillus* species by the CLSI method but not by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method. Please note that this information is based on testing of small number of isolates.

Against isolates of the Mucorales [*Lichtheimia* (*Absidia), Cunninghamella, Mucor, Rhizomucor,* and *Rhizopus* species], the activity of isavuconazole was variable (Table 1). Isavuconazole appears to more active than voriconazole but less active (4- to 16-fold) than posaconazole or amphotericin B.

Activity of isavuconazole in combination with other antifungal drugs

A combination of isavuconazole and micafungin, *in vitro*, showed no antagonism against the strains of *A. fumigatus, A. flavus,* and *A. terreus* tested*;* the activity of the combination of isavuconazole and amphotericin B could be antagonistic depending on the *Aspergillus* species and/or drug concentrations.

Activity of the combination of isavuconazole and micafungin showed indifferent or additive activity against the strains of *Cunninghamella bertholettiae, Rhizopus oryzae, Rhizopus microsporus,* and *Mucor circinelloides* tested; however, against *Lichtheimia corymbifera* strain, the activity was shown to vary from synergy to antagonism depending on the drug concentrations. A combination of isavuconazole and amphotericin B could be antagonistic depending on the Mucorales species and/or drug concentrations.

The clinical relevance of these findings is not known.

Drug resistance

There is a potential for development or resistance to isavuconazole. An increase in isavuconazole MICs, like other triazoles, is likely due to multiple mechanisms involving substitutions in the target gene *cyp51,* alterations in sterol profile, and/or efflux pump activity. For *Rhizopus* isolates, changes in sterol profile were associated with increased MIC and there was no change in activity of efflux pumps. For *Aspergillus* and *Fusarium* isolates, increased MICs were associated with elevated activity of efflux pumps. These observations are based on testing of a small number of isolates. The clinical relevance of these findings is not known.

Cross resistance

Isavuconazole MICs were higher against strains of *A. fumigatus* with reduced susceptibility to other azoles suggesting cross resistance. Such changes tended to mirror changes in voriconazole susceptibility. The increased MICs were observed in isolates with L98, TR34/L98H, M220, or G138/Y431/G434/G448 mutations in *cyp51* but not G54 mutation which confers resistance to itraconazole and posaconazole. The clinical relevance of such findings is not known.

Activity in Animal Models

<u>Aspergillosis</u>

The activity of isavuconazonium was measured in:

- mice with disseminated aspergillosis. Animals were infected with *A. flavus* (neutropenic mice), *A. fumigatus* (neutropenic and non-neutropenic mice) or *A. terreus* (neutropenic mice) as well as

- immunocompromised mice, guinea pigs and rabbits with pulmonary aspergillosis. Animals were infected with *A. fumigatus* strains.

In all animal models, except for the guinea pig pulmonary aspergillosis model, isavuconazonium was effective in improving survival and/or reducing fungal burden in animals infected with *A. flavus* or *A. fumigatus*. Such an effect was dose-dependent. The activity may decrease with a delay in time of initiation of treatment. In *A. terreus* infected mice, isavuconazonium was not effective under the experimental conditions tested.

Pharmacokinetic (PK) parameters were measured in some of the studies. In the *A. flavus* neutropenic murine model of disseminated aspergillosis, a ratio of 24 hour AUC/MIC in excess of 1 were obtained after treatment with ≥15 mg/kg/dose isavuconazole.

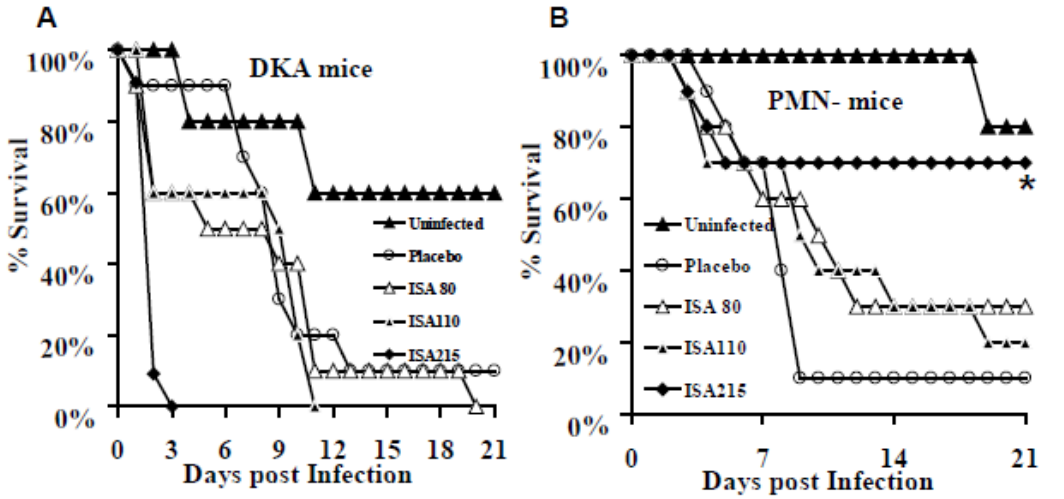
In the *A. fumigatus* neutropenic and non-neutropenic murine models, AUC/MIC appeared to be the driver of efficacy. In a non-neutropenic model of disseminated aspergillosis, the target attainment based on AUC/MIC using a pharmacodynamic (PD) marker of 14-day survival was 50.5. However, in an immunocompromised pulmonary aspergillosis model, the target attainment based on AUC/MIC using a PD marker of a one-log reduction in fungal burden on Day 7, by PCR, to achieve static effect was 503. In an immunocompromised rabbit model of pulmonary aspergillosis, isavuconazole doses equivalent to 40 or 60 mg/kg/day (which corresponds to exposure levels of 141.4 and 197.4 mcg·h/mL, respectively), were associated with prolonged survival, lower pulmonary fungal burdens and reduced lung injury compared with untreated controls. Each model utilized different endpoints to estimate PD target required for the exposure-response relationship.

In one study in neutropenic mice infected with *A. fumigatus*, T>MIC, rather than AUC, was thought to be the parameter that best described the *in vivo* antifungal activity of isavuconazole.

Mucormycosis

The activity of isavuconazonium was measured in neutropenic and diabetic ketoacidotic (DKA) ICR mice infected by the inhalational (pulmonary infection model of mucormycosis) or intravenous (hematogenously disseminated infection model of mucormycosis) route with a strain of *Rhizopus oryzae*. In the pulmonary infection model, isavuconazonium at the highest dose (215 mg/kg) tested, administered 8 hours post-exposure with 4.1×10^3 spores, was effective in improving survival of neutropenic infected mice (Figure 1B) but not of DKA infected mice (Figure 1A). However, in another experiment in DKA mice challenged with a lower inoculum concentration (2.4×10^3 spores), a trend towards increased survival was observed after treatment with isavuconazonium at a dose of 110 mg/kg three times daily compared with a placebo group of mice.

Figure 1: Survival rates of uninfected, placebo-treated and isavuconazonium treated in murine models of mucormycosis pneumonia (A) DKA mice and (B) neutropenic mice

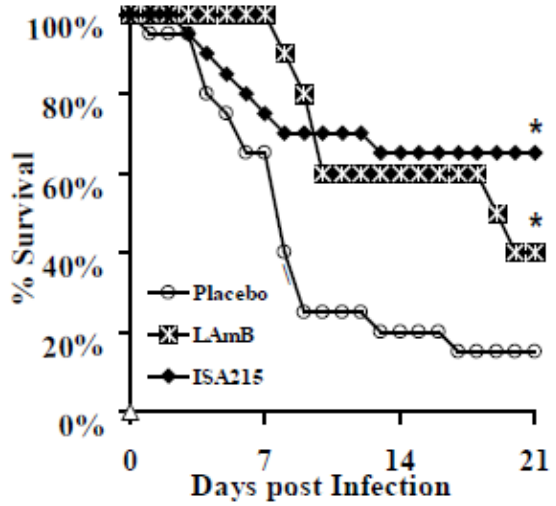


Mice (n=10 per arm) were infected intra-tracheally with 4.1 x 10^3 spores (for both neutropenic and DKA mice). Isavuconazonium treatment started 8 hours post infection and continued three times daily at 80, 110, or 215 mg/kg by oral gavage through D +4 post infection. Placebo mice were infected and treated with sterile water. * $P<0.05$ compared to placebo-treated mice by Log Rank test.
Source: New Drug Application [Ibrahim AS (2013) Isavuconazole therapy for treatment of murine mucormycosis. Internal report 9766-PH-0206]

In another experiment in neutropenic mice, the activity of isavuconazonium (215 mg/kg, orally, three times daily) was compared with high dose liposomal amphotericin B (15 mg/kg, once daily by the intravenous route; considered to be the standard therapy in this model). The experimental design was the same as summarized above except that the inhaled inoculum concentration was 1.3 x 10^4 spores. It appears that for the fungal burden study, liposomal amphotericin B treatment was initiated 24 hours post-infection. The results showed isavuconazonium and liposomal amphotericin B were effective in improving survival (Figure 2A) and reducing fungal burden by about one $\log_{10}$ in the lungs and brain (Figure 2B) of infected mice; reduction in fungal burden appears to be more in brain than lungs under the experimental conditions tested.

Figure 2: Effect of treatment with placebo, isavuconazonium (ISA) or LAmB on the protection of neutropenic mice from mucormycosis after intra-tracheal *R. oryzae* infection

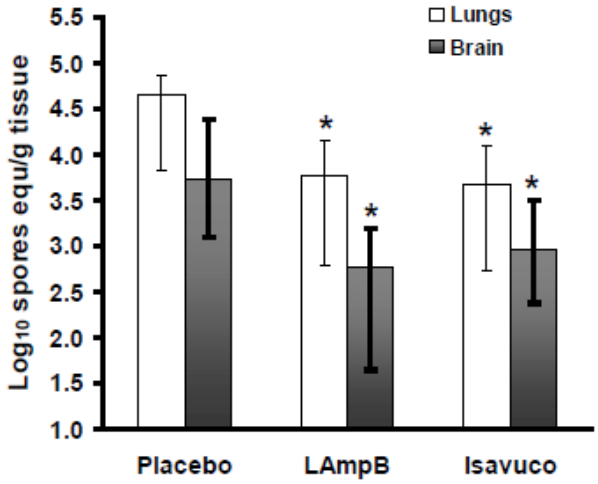
A: Survival



* P=0.025 or P=0.004 for LAmB or isavuconazonium compared to placebo by Log Rank test, respectively

Mice (n=20 per arm except for LAmB-treated mice in which n=10) were infected intra-tracheally with 1.3 x 10^3 spores. Isavuconazonium (215 mg/kg, t.i.d. by oral gavage) or LAmB (15 mg/kg qd by i.v. injection) treatment started 8 hours post-infection and continued through D +4 post-infection. Placebo mice were infected and treated with sterile water.

B: Lung and brain fungal burden



*P<0.05 compared to placebo by Wilcoxon Rank Sum test

Mice (n=9 per arm) were infected intra-tracheally with 1.3 x 10^3 spores. Isavuconazonium treatment started 8 hours post infection and continued three times daily at 215 mg/kg by oral gavage. LAmB treatment started 24 hours post infection at 15 mg/kg qd. Treatment was continued until D +3 post infection when mice were sacrificed and organ collected for tissue fungal burden by qPCR 1.

Source: New Drug Application [Ibrahim AS (2013) Isavuconazole therapy for treatment of murine mucormycosis. Internal report 9766-PH-0206]

Overall, the study suggests that isavuconazonium was effective in improving survival and reducing fungal burden in lungs and brain in DKA and neutropenic mice infected intra-tracheally with *Rhizopus oryzae*. Isavuconazonium was as effective as high dose liposomal amphotericin B in protecting neutropenic mice.

Isavuconazonium treatment was not effective in the hematogenously disseminated *R. oryzae* infection in the DKA and neutropenic models suggesting that the effectiveness may vary with the severity of infection and immune status of the host. Activity against Mucorales other than *R. oryzae* was not assessed.

6 NONCLINICAL TOXICOLOGY

The nonclinical toxicology program for isavuconazonium included in *vitro* and *in vivo* studies in mice, rats, monkeys, rabbits, hamsters and guinea pigs. The applicant evaluated the effects of oral isavuconazonium administration for up to 39 weeks in monkeys, 26 weeks in rats and 13 weeks in mice. In addition to general toxicology studies, there were evaluations of the genotoxic potential, fertility, embryo-fetal toxicity, pre- and postnatal development, local tolerance,

immunotoxicity and mechanistic studies. Study designs were appropriate and pivotal studies were conducted according to GLP.

There was good absorption of isavuconazonium after oral administration, with bioavailability between 62% (rats) and 87% (monkeys) after a single oral dose. Isavuconazonium was rapidly converted to isavuconazole by esterases, (predominately butylcholinesterase). Isavuconazole T_{max} was two hours in rats (three hours in monkeys) and the drug was eliminated with a $t_{½}$ of five hours in rats (10 hours in monkeys). *In vivo* studies indicate that CYP3A4, CYP3A5 and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazole. In some rat and monkey studies, there was evidence of induction of CYP3A and/or CYP2B.

Isavuconazole is extensively bound to proteins, with plasma protein binding above 96% for all species, including humans (99%). Tissue distribution was highest in the adrenal cortex and liver, followed by the small intestinal mucosa, brown fat, Harderian gland, pancreas, intra-orbital lacrimal gland, kidney cortex, adrenal medulla, stomach mucosa and the thyroid (in descending order). After administration to pregnant rats, isavuconazole was detected in the fetuses, in some instances at levels comparable to that in the maternal plasma. Isavuconazole is eliminated predominantly (over 80%) via the feces.

Liver findings

In repeat dose toxicology studies, isavuconazonium administration was associated with reversible increases in liver weights and/or hepatocellular hypertrophy in mice, rats and monkeys. Isavuconazole induced CYP3A and/or CYP2B, and therefore appears to be similar to other azole antifungal drugs which induce hepatocellular hypertrophy accompanied by an increase in activity of the hepatic microsomal drug metabolizing enzymes in the absence of any morphological evidence of hepatocellular damage. These liver findings were reversible at the end of a four week treatment-free period.

Thyroid findings

In rats, repeated administration of isavuconazonium was associated with an increase in thyroid weights and thyroid follicular cell hypertrophy/hyperplasia. These effects were not observed in monkeys. Since rats handle thyroid hormones differently from humans, it is not clear that these rat thyroid findings indicate any risk to humans.

Adrenal findings

Repeated administration of isavuconazonium to monkeys resulted in increases in adrenal weights and/or vacuolation/hypertrophy of adrenocortical cells. These changes were reversible. Although cholesterol levels were reduced in some instances, there were no atrophic or necrotic lesions. The clinical significance of these adrenal findings is unclear.

Embryo-fetal development findings

When administered to pregnant animals during early embryo-fetal development, isavuconazonium induced skeletal abnormalities and/or variations in the rat and rabbit at doses as low as one tenth of the systemic exposure at the clinical maintenance dose of 200 mg/day.

Skeletal abnormalities have also been associated with exposure to other azole antifungal drugs (such as ketoconazole and fluconazole) during pregnancy. When dams were dosed orally during pregnancy and through the weaning period, there was increased perinatal mortality among rat pups at doses about one half of the systemic exposure at the clinical maintenance dose of 200 mg/day. Isavuconazole was detected in the milk of lactating dams at levels up to 17 times higher than plasma levels.

7 SOURCES OF CLINICAL DATA

The isavuconazonium development program included 40 phase 1 studies, two phase 2, and two phase 3 trials. The indication of invasive aspergillosis is primarily supported by data from the phase 3 trial, 9766-CL-0104, a randomized, double-blind, active-controlled non-inferiority study. Patients with suspected invasive fungal disease and renal impairment (GFR < 50 ml/min) were allowed to enroll in Trial 9766-CL-0103, an open-label, uncontrolled study. Patients with renal impairment were excluded from the controlled trial due to the presence of a cyclodextran excipient in IV voriconazole. A subgroup of 37 patients was identified within the modified intent to treat population of trial 9766-CL-0103 (Mucorales - mITT population) to support the indication of invasive mucormycosis. Natural history data from the scientific literature were used as a basis of comparison. The applicant also presented an analysis of matched, actively treated control patients from the Fungiscope Registry as supportive evidence. The phase 1 and 2 data contributed to the analyses of safety, but not efficacy. The phase 2 and 3 trials are summarized below, in Table 2:

Table 2: Summary of Isavuconazonium Phase 2 and Phase 3 Trials

Parameter	Phase 3 Trials		Phase 2 Trials	
	9766-CL-0104 (WSA-CS-004)	**9766-CL-0103 (WSA-CS-003)**	**9766-CL-0101 (WSA-CS-001)**	**9766-CL-0102 (WSA-CS-002)**
Design	Double-blind, randomized, non-inferiority study to evaluate efficacy and safety of ISA vs VRC for the primary treatment of IFD caused by *Aspergillus* spp. or other filamentous fungi	Open-label, non-comparative study to evaluate the safety and efficacy of ISA for the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare molds, yeasts or dimorphic fungi	Randomized, double-blind, phase 2, parallel group, non-inferiority study to compare the efficacy and safety of 3 oral dosing regimens of ISA to a standard oral FLU regimen for the treatment of patients with uncomplicated esophageal candidiasis	Open-label, multicenter study of the safety and efficacy of escalating intravenous and oral ISA in the prophylaxis of patients undergoing chemotherapy for AML
No. of Sites	102	34	8	3
Countries with Sites that Enrolled Patients	Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Egypt, France, Germany, Hungary, India, Israel, Italy, Malaysia, Mexico, The Netherlands, New Zealand, Poland, Russia, South Korea, Spain, Switzerland, Thailand, Turkey and the United States	Belgium, Brazil, Germany, India, Israel, Lebanon, Mexico, Russia, South Korea, Thailand and the United States	South Africa	Germany
Treatment Groups	ITT: ISA (n = 258) SAF: ISA (n = 257)	ITT: VRC (n = 258) SAF: VRC (n = 259)	ITT/SAF: ISA (n = 146) RI (n = 59) NRI (n = 87)	Safety Population: ISA A (n = 40) ISA B (n = 40) ISA C (n = 41) FLU D (n = 38)	Safety Population: Group 1: (n = 11) Group 2: (n = 12)
Loading Dose	ISA 200 mg administered q8h IV for 2 days	VRC 6 mg/kg administered q12h IV for 1 day	ISA 200 mg q8h IV or oral on days 1 and 2	ISA A: 200 mg day 1 ISA B: 400 mg day 1 ISA C: 400 mg day 1 FLU D: 200 mg day 1	Group 1: 400/200/200 mg day 1, 200/200 mg day 2 Group 2: 800/400/400 mg day 1, 400/400 mg day 2
Maintenance Dose	200 mg once per day IV or oral	4 mg/kg q12h IV or 200 mg q12h oral	ISA 200 mg q24h IV or oral from day 3 to EOT	ISA A: 50 mg/day ISA B: 400 mg/week ISA C: 100 mg/day FLU D: 100 mg/day	Group 1: 200 mg/day Group 2: 400 mg/day

Table continued on next page

Parameter	Phase 3 Trials		Phase 2 Trials	
	9766-CL-0104 (WSA-CS-004)	**9766-CL-0103 (WSA-CS-003)**	**9766-CL-0101 (WSA-CS-001)**	**9766-CL-0102 (WSA-CS-002)**
Patient Population	Patients with IFD caused by *Aspergillus* or other filamentous fungi	Renally impaired (creatinine clearance < 50 mL/min) patients with invasive aspergillosis and patients with IFD caused by other rare molds, yeasts or dimorphic fungi	Patients with uncomplicated esophageal candidiasis	Neutropenic AML patients who were entering first induction treatment or subsequent chemotherapy and had not experienced a prior invasive fungal infection
Primary efficacy endpoint	All-cause mortality rate through day 42	DRC-assessed overall response at day 42	Endoscopically confirmed clinical response at EOT	Rate of microbiological success (absence of break-through fungal infections and lack of need for other systemic AFT)
Secondary efficacy variables	• Key secondary: DRC-assessed overall response at EOT • All-cause mortality through day 84 • DRC-assessed overall response at days 42 and 84 • Clinical, mycological and radiological response at EOT, and days 42 and 84	• DRC-assessed overall response at EOT and day 84 • DRC-assessed clinical, mycological and radiological success at EOT and days 42 and 84 • Survival rate by days 42, 84, 120 and 180	• Overall therapeutic response at EOT • Microbial response at EOT • Relapse rate at the follow-up and late follow-up visits in patients assessed as a success (cure) at EOT, after a 14-day or 21-day treatment regimen	none

Study 9766-CL-0103: The ITT and SAF were identical and consisted of all enrolled patients who received at least one dose of study medication.

Study 9766-CL-0104: The ITT consisted of all randomized patients who received at least one administration of study drug (data were analyzed by the treatment a patient was randomized to). The SAF population consisted of all randomized patients who received at least one dose of study drug (data were analyzed according to the study drug that patients received as the first dose even if it was different from what they were randomized to).

AFT: antifungal therapy; AML: acute myeloid leukemia; DRC: Data Review Committee; EOT: end of treatment; FLU: fluconazole; IFD: invasive fungal disease; ISA: isavuconazonium; ITT: intent-to-treat; MIC: minimum inhibitory concentration; NRI: non-renally impaired; RI: renally impaired; SAF: safety analysis set; VRC: voriconazole.

Source: Studies 9766-CL-0104, 9766-CL-0103, 9766-CL-0102 and 9766-CL-0101

Overview of Trial 9766-CL0104

Trial 9766-CL-0104 was a phase 3, randomized, multicenter, double-blind, non-inferiority, comparative group trial designed to evaluate the safety and efficacy of isavuconazonium versus voriconazole for the primary treatment of invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. The study was conducted at 102 centers worldwide. Eligible patients were men or women aged ≥ 18 years with proven, probable, or possible IFD based on diagnostic tests, the presence of host factors, radiological/clinical features, and mycological evidence[6]. Enrolled subjects were randomized in a 1:1 ratio to receive treatment with either isavuconazonium or voriconazole. Patients were stratified by geographic location (United States/Canada, Western Europe/Australia/New Zealand, and Other Regions), whether or not they underwent an allogeneic bone marrow transplant (BMT), and whether or not they had uncontrolled malignancy at baseline.

Patients randomized to receive isavuconazonium were to receive a loading dose of 200 mg three times daily IV for the first two days of treatment followed by a maintenance dose of 200 mg daily IV or oral from Day 3 to the end of treatment (EOT). Patients randomized to receive voriconazole were to receive a loading dose of 6 mg/kg twice IV in the first 24 hours of treatment followed by a maintenance dose of 4 mg/kg twice daily IV or 200 mg twice daily oral from Day 2 to EOT. The switch from IV to oral was to be made as early as possible from Day 3 but patients could remain on IV treatment for reasons such as inability to swallow, gastric suction, or concerns about adequate dosing. Patients were to receive treatment for a minimum of seven days after resolution of all clinical symptoms and physical findings of infection or for a maximum of 84 days.

An independent Data Review Committee (DRC) consisting of experts in infectious diseases was established to adjudicate the categorization of each patient's IFD at enrollment (including data up to Day 7 as relevant) and to evaluate clinical, mycological, radiological, and overall response at EOT, Day 42 and Day 84, as well as to assess attributable mortality. The patient profile data reviewed by the DRC did not include the investigator's assessments of baseline mycological criteria or response, or any adverse reactions that could potentially unblind the DRC. Independent radiologists were responsible for providing a qualitative assessment of radiology images including an overall impression of the images that described the size, number and characteristics of the IFD for each time point, as well as an overall outcome assessment of percent improvement from baseline at EOT, Day 42, and Day 84; this information was provided to the DRC.

The DRC categorized each patient's IFD at enrollment as proven, probable, possible, or no IFD/no invasive mold infection based on the presence of adequate host factors, the presence of adequate radiologic and clinical features, and mycological evidence from histopathology, culture, and/or galactomannan (GM).[6] Per the protocol, the DRC could assess a probable case of aspergillosis using GM if there were two consecutive serum GM values ≥ 0.5 or a single

[6] DePauw, B., Walsh, T.J., Donnelly, J.P., *et al.* Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clinical Infectious Diseases 2008;46(12):1813-21.

serum GM value ≥ 0.7. The Division conducted a review of published literature on GM and recommended the following cut-off values; a case can be assessed as probable aspergillosis if there are two consecutive serum GM values ≥ 0.5 or a single serum or bronchoalveolar lavage (BAL) GM value ≥ 1.0. Based on these criteria, a single serum GM value between 0.7 and 1.0 would be considered as possible aspergillosis.

The primary objective of the study was to assess non-inferiority of isavuconazonium compared to voriconazole in all-cause mortality through Day 42. The primary efficacy endpoint was the all-cause mortality rate through Day 42. The non-inferiority margin justification for all-cause mortality through day 42 was based on trials of voriconazole, demonstrating superiority over amphotericin B, as well as literature to derive historical estimates of mortality with placebo (no treatment) and amphotericin B effect. Based on this information, an estimate of the effect of voriconazole over placebo (M1) was approximately 58%, and the non-inferiority margin of 10% was acceptable, based on clinical judgment for M2. A key secondary efficacy endpoint was the DRC assessment of overall response at EOT. Based on available historical data, an estimate of M1 for this endpoint cannot be determined. Additional secondary efficacy endpoints included all-cause mortality through Day 84, DRC-assessed overall response at Day 42 and Day 84, as well as DRC-assessed rates at EOT, Day 42, and Day 84 of clinical response, mycological response, and radiological response individually.

Overall response was assessed by the DRC as complete, partial, stable, failure, or not done. A patient with complete or partial overall response was considered a success. Clinical response was assessed by the DRC as:

- Success - Resolution of all attributable clinical symptoms and physical findings OR partial resolution of attributable clinical symptoms and physical findings
- Failure - No resolution of any attributable clinical symptoms and physical findings and/or worsening
- Not applicable - No attributable signs and symptoms present at baseline and no symptoms attributable to IFD developed post baseline
- Not done.

Mycological response was assessed by the DRC as eradication, presumed eradication, persistence, presumed persistence, no mycological evidence available at baseline, or not done. A patient with eradication or presumed eradication was considered a success. Radiological response was assessed by the DRC as a success if there was improvement in radiological findings of at least 25% from baseline, if the assessment was made prior to Day 42, or at least 50% from baseline if the assessment was made after Day 42. An assessment of response was not made by the DRC if the DRC indicated that the patient had no IFD/no invasive mold infection at baseline.

The primary analysis of all-cause mortality through Day 42 was based on the difference in the rate (isavuconazonium-voriconazole) and corresponding 95% confidence interval calculated using the stratified Cochran-Mantel Haenszel (CMH) method. The stratification factors were geographical region, allogeneic bone marrow transplant (BMT) status, and uncontrolled malignancy status. The upper bound of the 95% confidence interval was compared to the justified non-inferiority margin of 10%. If the upper bound was less than 10%,

isavuconazonium was considered non-inferior to voriconazole with respect to all-cause mortality through Day 42. A patient with unknown survival status through Day 42 was included as a death in the calculation of the all-cause mortality rate through Day 42.

Analyses of the secondary endpoints related to rates were analyzed using the same method as the primary endpoint. A patient with unknown survival status through Day 84 was included as a death in the calculation of the all-cause mortality rate through Day 84. For the DRC-assessed endpoints, a patient that the DRC indicated as Not Done for a visit was considered as missing and was included as a failure for the visit.

The following populations were used for the efficacy analyses. The intent-to-treat (ITT) population included all randomized patients who received at least one administration of study drug. The modified ITT (mITT) population included ITT patients who had proven or probable IFD as determined by the DRC. Patients with an appropriate host factor and clinical features could be considered to have probable IFD based on the GM criteria per the protocol (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum GM value ≥ 0.7). The mITT-FDA population included ITT patients who had proven or probable IFD, however patients with appropriate host factor and clinical features could be considered to have probable IFD based on the GM criteria per current FDA recommendations (i.e., two consecutive serum GM values $\geq$ 0.5 or at least one serum or BAL GM value ≥ 1.0). The mycological ITT (myITT) population included mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture, or GM per the protocol and assessed by the DRC.

Overview of Trial 9766-CL-0103

Trial 9766-CL-0103 was designed to evaluate the safety and efficacy of isavuconazonium for the primary treatment of IFD caused by *Aspergillus* species in subjects with renal impairment, or rare filamentous fungi. An open-label design was selected due to the inherent difficulty of enrolling sufficient numbers of patients for diseases with a low prevalence, such as invasive mucormycosis. This multicenter study was conducted at 34 centers globally including sites in the US, European Union (EU), South America, Asia and the Middle East. The trial was conducted over a six year period from April, 2008 to January, 2014.

The Inclusion and Exclusion Criteria were similar to Trial 9766-CL-0104, except patients with rare fungal infections were enrolled regardless of renal function.

Similar to Trial 9766-CL-0104, isavuconazonium was administered interchangeably via IV or oral formulations, and in the latter case without regard to food intake. An IV isavuconazonium loading regimen was administered during the first 48 hours (200 mg q8h) followed by a maintenance dose from Day 3 to EOT (200 mg q24h). The dose chosen for this study was identical to the dose administered in the phase 3 trial for invasive aspergillosis (Study 9766-CL-0104). Patients who were enrolled under Amendment 1 (October 16, 2007; 6 patients) were treated up to a maximum period of 84 days, whereas, most patients who were enrolled from Amendment 3 onwards (November 17, 2010) were treated up to a maximum period of 180 days. An allowance was made to extend isavuconazonium dosing beyond 180 days under country-specific Amendment 4 (April 12, 2012 for US, Israel and Belgium), based on investigator

request and sponsor approval, for patients who demonstrated clinical improvement while on isavuconazonium and for whom isavuconazonium was deemed the best therapeutic choice.

Survival status was recorded at Day 42, Day 84 and 4 weeks after the last administration of study drug. An additional follow-up visit 8 weeks after EOT was made if adverse reactions were still ongoing at the 4-week follow-up visit. The DRC and investigators evaluated the clinical response to treatment for patients at Day 42, Day 84 and EOT. Baseline mycological assessment (screening through Day 7) of the patient's invasive fungal disease (IFD) status was performed according to best local practice using local and central laboratories, including suitable samples for fungal culture as well as samples from the infected site for histology and cytology. Baseline radiological assessments of IFD were performed during the screening period. The European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 definitions of IFD were used. Mycological and radiological assessments were also performed at Day 42, Day 84 and EOT. A DRC, which consisted of clinicians in the field of fungal infections, was established to conduct a data review for all patients who received at least one dose of study drug. The DRC adjudicated, independently from the sponsor and the study investigators, the categorization of the IFD and evaluated clinical, mycological, radiological and overall responses at Day 42, Day 84 and EOT. The DRC also assessed location of disease, therapy status (i.e., primary, refractory or intolerant) and attributable mortality.

The investigator evaluated safety by monitoring treatment-emergent adverse reactions and findings from physical examination (including eye exam), vital signs, laboratory tests, 12-lead electrocardiogram (ECG) and concomitant medication/surgery.

The study protocol identified the DRC-assessed overall response as the primary endpoint. However, both the applicant and the FDA agree that 42-day mortality is the most relevant primary endpoint. DRC-assessed overall responses at EOT were therefore analyzed as secondary efficacy outcomes. Additional DRC assessments included clinical, mycological and radiological response at Day 42, Day 84 and EOT.

8 EVALUATION OF EFFICACY

8.1 Invasive Aspergillosis

8.1.1 Patient Disposition, Demographic and Baseline Characteristics

Overall, 527 patients were randomized into the trial: 263 to the isavuconazonium group and 264 to the voriconazole group. Eleven patients were randomized but did not receive any dose of study medication. Therefore, the ITT population consisted of 516 patients (258 in each treatment group). Out of the 516 patients in the ITT population, 244 subjects were excluded from the mITT population because the DRC assessed the patient as having either possible or no IFD at baseline. While there is only a net difference of three patients between the mITT and mITT-FDA populations, the mITT-FDA population includes 20 patients who were considered probable invasive aspergillosis based on a BAL GM $\geq$ 1.0 but excludes 17 patients who were

considered probable invasive aspergillosis in the mITT population based on a single serum GM between 0.7 and 1.0.

The following table summarizes the demographic and baseline characteristics of the ITT population.

Table 3: Analysis Populations, Trial 9766-CL-0104

	Isavuconazonium	Voriconazole
Randomized	263	264
ITT	258	258
mITT	143	129
Aspergillus species only*	49 (34.3)	39 (30.2)
Aspergillus species plus other mold species*	3 (2.1)	1 (0.8)
Non-Aspergillus species only	5 (3.5)	6 (4.7)
Mold species not otherwise specified (NOS)	14 (9.8)	15 (11.6)
No pathogen identified**	72 (50.3)	68 (52.7)
mITT-FDA	147	128
myITT	123	108
Probable by serum GM only	71 (57.7)	68 (63.0)
Proven or probable Aspergillosis by culture or histology	52 (42.3)	40 (37.0)

**A. fumigatus* and *A. flavus* were the most common pathogens identified. There were less than 7 patients with other *Aspergillus* species (*A. niger*, *A. sydowi*, *A. terreus*, and *A. westerdijkiae*).

**Probable based on GM with the exception of 1 isavuconazonium subject who was based on a culture from a non-sterile site and had adequate host factors and clinical and radiological factors

Overall, 60% of the study population was male and 78% was white. The mean age of the patients was 51 years. The majority of the patients had hematologic malignancy as their underlying condition. The overall distribution of geographic region was: 11% US/Canada, 41% Western Europe/Australia/New Zealand, and 48% all other regions (Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand, and Turkey). Approximately 20% of patients had a prior allogeneic HSCT and 70% had an uncontrolled malignancy at baseline. Approximately 66% of patients were neutropenic at baseline, 17% had corticosteroid use, and 43% had T-cell immunosuppressant use at baseline.

Table 4: Demographic and Baseline Characteristics (ITT), Trial 9766-CL-0104

	Isavuconazonium	Voriconazole
# Patients	258	258
Gender		
Male	145 (56.2)	163 (63.2)
Female	113 (43.8)	95 (36.8)
Age mean (SD)	51.1 (16.2)	51.1 (15.8)
Min, max	17, 82	18, 87
Race		
White	211 (81.8)	191 (74.3)
Black	1 (0.4)	1 (0.4)
Asian	45 (17.4)	64 (24.9)
Other	1 (0.4)	1 (0.4)
Missing	-	1 (0.4)
Geographic Region		
US/Canada	30 (11.6)	28 (10.9)

Western Europe/Australia/New Zealand	105 (40.7)	107 (41.5)
Other Region	123 (47.7)	123 (47.4)
Hematologic Malignancy	211 (81.8)	222 (86)
Prior Allogeneic BMT	54 (20.9)	51 (19.8)
Uncontrolled Malignancy at Baseline	173 (67.1)	187 (72.5)
Neutropenic at Baseline	163 (63.2)	175 (67.8)
Use of Corticosteroids	48 (18.6)	39 (15.1)
Use of T-cell Immunosuppressant	111 (43.0)	109 (42.2)

8.1.2 Analysis of All-Cause Mortality

The primary efficacy endpoint was all-cause mortality through Day 42. All-cause mortality through Day 84 was assessed as a secondary endpoint. The all-cause mortality rates for the various ITT-related populations are presented in Table 5. The ITT population was the protocol defined primary analysis population for all-cause mortality through Day 42. In the ITT population, the all-cause mortality rate through Day 42 was 18.6% for isavuconazonium and 20.2% for voriconazole. The adjusted difference between treatment groups was -1.0% with a corresponding 95% confidence interval of (-8.0, 5.9). Since the upper bound of the 95% confidence interval is less than 10%, non-inferiority of isavuconazonium compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42. Day 42 survival status was known for all but three isavuconazonium and two voriconazole ITT patients who are imputed as deaths in these analyses. The results are robust across the various populations and are similar regardless of whether the protocol-defined or FDA-defined galactomannan criteria are used for defining the mITT population. The adjusted treatment difference for the various populations with proven or probable IFD/aspergillosis ranged from -2.7% to -2.1%. The upper bounds of the 95% confidence interval around the adjusted treatment difference across these populations ranged from 7.3% to 8.2% and are all lower than the 10% non-inferiority margin.

Table 5: All-Cause Mortality, Trial 9766-CL-0104

Timepoint	Population	Isavuconazonium	Voriconazole	Difference and 95% CI*
Through Day 42	ITT**	48/258 (18.6)	52/ 258 (20.2)	-1.0 (-8.0, 5.9)
	mITT	28/143 (19.6)	30/129 (23.3)	-2.6 (-12.6, 7.3)
	mITT-FDA	28/147 (19.0)	28/128 (21.9)	-2.1 (-11.9, 7.7)
	myITT	23/123 (18.7)	24/108 (22.2)	-2.7 (-13.6, 8.2)
Through Day 84	ITT***	75/258 (29.1)	80/258 (31.0)	-1.4 (-9.2, 6.4)
	mITT	43/143 (30.1)	48/129 (37.2)	-5.5 (-16.3, 5.4)
	mITT-FDA	41/147 (27.9)	43/128 (33.6)	-4.7 (-15.4. 6.0)
	myITT	35/123 (28.5)	39/108 (36.1)	-5.7 (-17.5, 6.0)

*adjusted difference (Isa - Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status. The confidence intervals presented are slightly different from those presented by the applicant due to the method of calculation and the conclusions drawn are the same.

**survival status unknown for only 3 isavuconazonium and 2 voriconazole ITT subjects

*** survival status unknown for only 3 isavuconazonium and 5 voriconazole ITT subjects

8.1.3 Analysis of DRC-Assessed Overall Response

DRC-assessed overall response at EOT was a key secondary endpoint. For the mITT population, the DRC-assessed overall response rates at EOT were similar between treatment groups (35% for isavuconazonium and 36.4% for voriconazole). The lower bound of the 95%

confidence interval about the adjusted treatment difference is -12.8%. Complete response was seen in 11.9% isavuconazonium patients and 10.1% voriconazole patients. Partial response was seen in 23.1% isavuconazonium patients and 27.8% voriconazole patients. The results for the mITT-FDA population are similar to that of the mITT population. The results for the myITT population are also similar with a slightly higher DRC-assessed overall response at EOT for voriconazole patients as compared to isavuconazonium patients.

Table 6: DRC-assessed Overall Response at EOT, Trial 9766-CL-0104

	Isavuconazonium	Voriconazole	Difference and 95% CI*
mITT- Success	50/143 (35.0)	47/129 (36.4)	-1.6 (-12.8, 9.6)
Complete	17 (11.9)	12 (10.1)	
Partial	33 (23.1)	34 (26.3)	
Stable	42 (29.4)	33 (25.6)	
Progression	51 (35.7)	49 (38.0)	
mITT-FDA - Success	52/147 (35.4)	47/128 (36.7)	-1.8 (-12.9, 9.3)
Complete	19 (12.9)	14 (10.9)	
Partial	33 (22.5)	33 (25.8)	
Stable	43 (29.3)	34 (26.6)	
Progression	52 (35.4)	47 (36.7)	
myITT- Success	43/123 (35.0)	42/108 (38.9)	-4.0 (-16.3, 8.4)
Complete	13 (10.6)	12 (11.1)	
Partial	30 (24.4)	30 (27.8)	
Stable	36 (29.3)	29 (26.9)	
Progression	44 (36.8)	37 (34.4)	

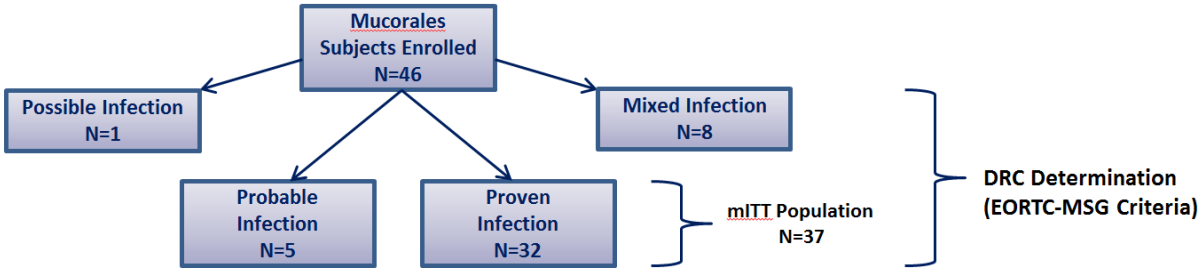
* adjusted difference (Isavuconazonium - Voriconazole) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status. The confidence intervals presented are slightly different from those presented by the applicant due to method of calculation. The conclusions drawn are the same.

8.2 Invasive Mucormycosis

8.2.1 Demographics

This multicenter study was conducted at 34 centers globally including sites in the US, EU, South America, Asia and the Middle East. A total of 149 patients with a variety of fungal infections were enrolled in the study. Of these, 146 patients (98.0%) received at least one dose of study drug and were included in the ITT population. The population considered for the proposed indication consists of 37 mITT-Mucorales patients identified as having Mucorales only. Figure 3 depicts a flowchart of the study population.

Figure 3: Flow Chart of the Mucorales Study Population, Trial 9766-CL-0103



Source: FDA Reviewer Generated from Study Report 9766-CL-0103

The Mucorales mITT population was further stratified by treatment status. The primary treatment group was defined as those patients who received isavuconazonium as initial antifungal therapy, and the remaining two groups were considered salvage therapy. The refractory treatment group was identified by the progression of disease while on antifungal therapy at enrollment, and the intolerant treatment group either failed to achieve therapeutic drug levels or experienced significant drug related adverse reactions. The categorization of the 37 mITT-Mucorales patients is summarized in Table 7.

Table 7: Distribution of patients by DRC adjudicated infection status and treatment group.

	Proven N=32	Probable N=5	Possible N=1
Primary N=22	18 (47.4%)	3 (7.9%)	1 (2.6%)
Refractory N=11	10 (26.3%)	1 (2.6%)	0
Intolerant N=5	4 (10.5%)	1 (2.6%)	0

Source: FDA Reviewer Generated from Study Report 9766-CL-0103

The median age of mITT-Mucorales patients was 50 years and the majority of patients were ≤ 65 years (86.5% overall), with 8.1% of patients being over 75 years of age. The majority of patients were male (81.1%), and White (67.6%). A summary of demographics and baseline characteristics by therapy status is presented in Table 8. The mITT-Mucorales subgroup had a majority of patients with hematologic malignancy (59%) at baseline, which was a greater proportion than found in the reference epidemiology studies (44% and 17%, respectively).

Table 8: Summary of Demographic and Baseline Characteristics by Therapy Status (mITT-Mucorales Population - Study 9766-CL-0103)

	Primary	Refractory	Intolerant	Total
Age (years)				
N	21	11	5	37
Mean (SD)	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)
Min	25	22	23	22
Median	51.0	50.0	42.0	50.0
Max	77	79	57	79
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age category (years)				
≤ 45	5 (23.8%)	5 (45.5%)	3 (60.0%)	13 (35.1%)
> 45 - ≤ 65	12 (57.1%)	5 (45.5%)	2 (40.0%)	19 (51.4%)
> 65	4 (19.0%)	1 (9.1%)	0	5 (13.5%)
Gender				
Male	17 (81.0%)	8 (72.7%)	5 (100.0%)	30 (81.1%)
Female	4 (19.0%)	3 (27.3%)	0	7 (18.9%)
Race				
White	12 (57.1%)	10 (90.9%)	3 (60.0%)	25 (67.6%)
Black or African American	1 (4.8%)	1 (9.1%)	2 (40.0%)	4 (10.8%)
Asian	8 (38.1%)	0	0	8 (21.6%)
Other	0	0	0	0
Ethnicity				
Hispanic or Latino	1 (4.8%)	0	0	1 (2.7%)
Not Hispanic or Latino	20 (95.2%)	11 (100.0%)	5 (100.0%)	36 (97.3%)
eGFR-MDRD category (mL/min/1.73m^2)				
< 60	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
≥ 60	15 (71.4%)	8 (72.7%)	3 (60.0%)	26 (70.3%)
Geographic region				
United States	7 (33.3%)	4 (36.4%)	5 (100.0%)	16 (43.2%)
Western Europe (Bel and Ger)	1 (4.8%)	4 (36.4%)	0	5 (13.5%)
Other Regions†	13 (61.9%)	3 (27.3%)	0	16 (43.2%)

† Other regions includes Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel

Source: Reviewer Generated from a manual review of case reports from Trial 9766-CL-0103

Table 9 presents underlying host factors for mITT-Mucorales population in comparison to two published epidemiologic studies.

Table 9: Comparative Underlying Host Factors in the mITT-Mucorales Population

	Study 9766-CL-0103	Skiada et al (2011)[3]	Roden et al (2005)[2]
Hematologic Malignancy	22/37 (59%)	102/230 (44%)	154/929 (17%)*
Neutropenia at baseline	10/37 (43%)	N/D	N/D
Bone Marrow Transplant†	13/37 (35%)	21/230 (9%)	44/929 (5%)
Diabetes mellitus	4/37 (11%)	39/230 (17%)	337/929 (36%)
Solid Organ Transplant	3/37 (8%)	10/230 (4%)	61/929 (7%)
Solid Organ Malignancy	2/37 (5%)	11/230 (5%)	N/D*
Other#	3/37 (8%)	0	0
Aplastic Anemia	1/37 (3%)	4/230 (2%)	N/D
No Underlying Disease	1/37 (3%)	0/230 (0%)	176/929 (19%)
Burn/Trauma	0/37 (0%)	46/230 (20%)	43/176 (24%)

N/D: Not Determined
*Malignancy not differentiated between solid organ and hematologic origins.
†BMT not distinguished between allogeneic and autologous transplant
Two patients with chronic steroid use (Ulcerative Colitis and COPD), and a third with Klippel-Trenaunay-Weber Syndrome (a congenital vascular disease involving lymphatics)
Neutropenia was defined as ANC $< 0.5 \times 10^9$/L ($< 500/mm^3$).
Source: Reviewer Generated

The site of infection was adjudicated by the DRC. Site of infection is further described in Table 10, below and Figure 4 on the following page.

Table 10: DRC Assessment of IFD Locations at Baseline by Therapy Status

	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Disseminated Disease				
Yes	8 (38%)	2 (18%)	1 (20%)	11 (30%)
No	12 (62%)	9 (82%)	4 (80%)	26 (70%)
Location				
LRTD * Only	1 (5%)	5 (46%)	4 (80%)	10 (27%)
LRTD Plus other organ	8 (38%)	3 (27%)	1 (20%)	12 (32%)
Non LRTD Only	12 (57)	3 (27%)	0	15 (41%)
Non-LRTD Location				
Bone	4 (19%)	0	1 (20%)	5 (14%)
CNS	6 (29%)	0	0	6 (16%)
Deep Soft Tissue (e.g. Muscle)	1 (5%)	2 (18%)	0	3 (8%)
Eye	7 (33%)	0	0	7 (19%)
GI Tract	2 (10%)	0	0	2 (5%)
Kidneys	2 (10%)	0	0	2 (5%)
Liver	2 (10%)	0	0	2 (5%)
Sinus	13 (62%)	3 (27%)	0	16 (43%)
Skin	2 (10%)	0	0	2 (5%)
Spleen	1 (5%)	0	0	1 (3%)

*LRTD: Lower Respiratory Tract Disease

Source: FDA reviewer generated from a manual review of case reports from Trial 9766-CL-0103

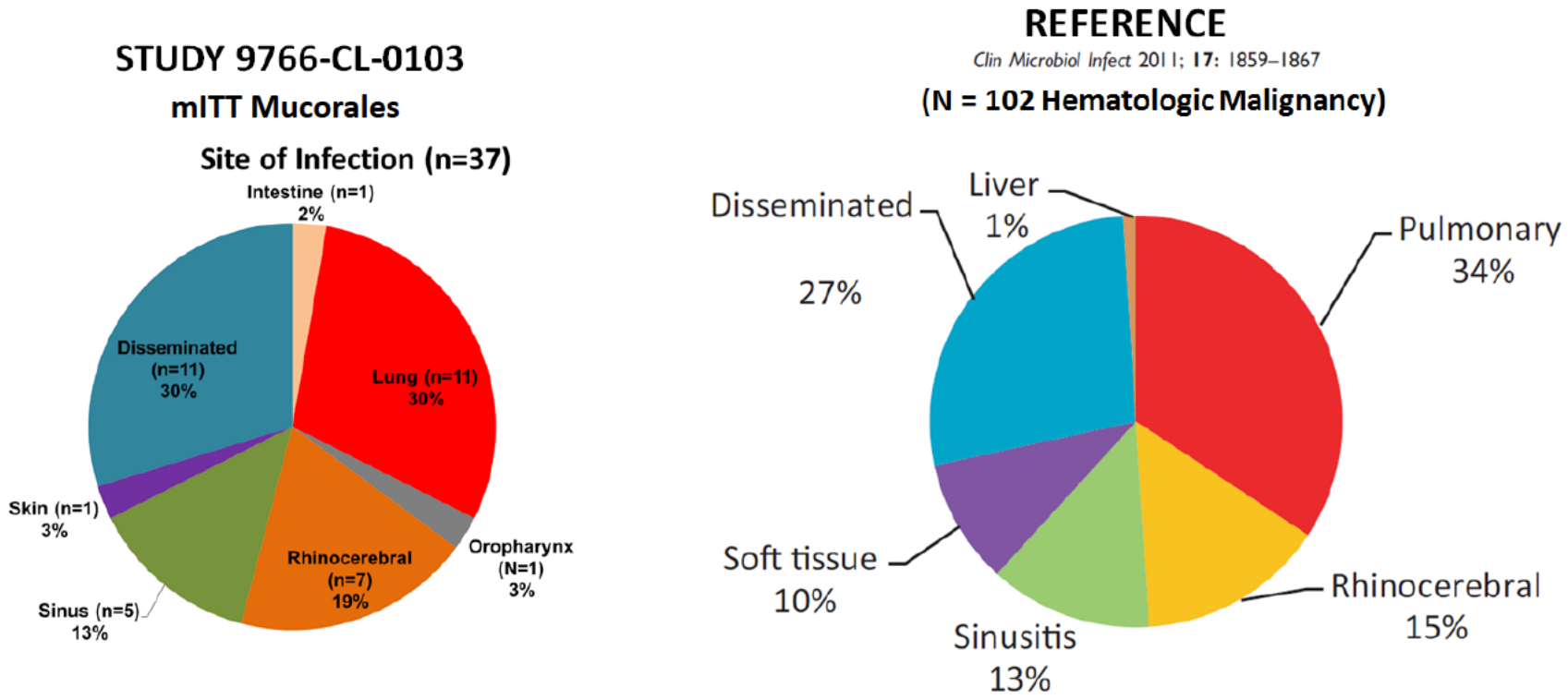
The three most commonly reported pathogens at baseline, as assessed by the DRC, were Mucormycetes NOS (35.1%) and *Mucor* NOS and *Rhizopus oryzae*, (both reported in 18.9% of patients). For primary therapy patients, the three most commonly reported pathogens at baseline, as assessed by the DRC, were *Mucor* NOS (33.3%), Mucormycetes NOS (28.6%) and *Rhizopus oryzae* (19.0%). The isolates are summarized in Table 11.

Table 11: DRC Assessment of Pathogen Causing IFD at Baseline in the mITT-Mucorales Study Population

	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Pathogen				
Mucormycetes NOS	6 (28.6%)	5 (45.5%)	2 (40.0%)	13 (35.1%)
Mucor NOS	7 (33.3%)	0	0	7 (18.9%)
Rhizopus oryzae	4 (19%)	3 (27.3%)	0	7 (18.9%)
Rhizomucor	2 (9.5%)	2 (18.2%)	1 (20.0%)	5 (13.5%)
Lichtheimia corymbifera	2 (9.5%)	0	0	2 (5.4%)
Rhizopus NOS	0	1 (9.1%)	1 (20.0%)	2 (5.4%)
Cunninghamella	0	0	1 (20.0%)	1 (2.7%)

Source: Modified from Applicant Study Report 9766-CL-0103

Figure 4: Location of Primary Infection Site, Study 9766-CL-0103 mITT-Mucorales Population, Compared to Reference



Source: FDA Reviewer Generated

Study Drug Exposure: In mITT-Mucorales patients and primary therapy patients, respectively, the median duration of study drug therapy was 84 days (range 2 to 882) and 102 days (range 2 to 882), with the median duration of intravenous treatment being 10 and 9.5 days.

8.2.2 Patient Disposition

Table 12 summarizes the disposition of the mITT-Mucorales study population.

Table 12: Primary Reason for Treatment and Study Discontinuation

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation				
Completed	6 (28.6%)	2 (18.2%)	3 (60%)	11 (29.7%)
Discontinued	13 (61.9%)	9 (81.8%)	2 (40%)	24 (64.9%)
Primary reason for discontinuation				
Death	6 (28.6%)	3 (27.3%)	2 (40%)	11 (29.7%)
Adverse event/intercurrent illness	2 (9.5%)	4 (36.4%)	0	6 (16.2%)
Did not cooperate	3 (14.3%)	1 (9.1%)	0	4 (10.8%)
Insufficient therapeutic response	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Admin/other	1 (4.8%)	0	0	1 (2.7%)
Discontinuation during follow-up period				
Completed	7 (33.3%)	3 (27.3%)	2 (40%)	12 (32.4%)
Discontinued	12 (57.1%)	8 (72.7%)	3 (60%)	23 (62.2%)
Primary reason for discontinuation				
Death	10 (47.6%)	6 (54.5%)	2 (40%)	18 (48.6%)
Admin/other	0	1 (9.1%)	1 (20%)	2 (5.4%)
Withdrew consent	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Failure to return/lost to follow-up	1 (4.8%)	0	0	1 (2.7%)
Ongoing‡	2 (9.5%)	0	0	2 (5.4%)

‡ Patients who were still actively receiving study treatment as of September 30, 2013.

Source: FDA reviewer generated from dataset for Study 9766-CL-0103

8.2.3 Analysis of Primary Endpoints

The primary efficacy endpoints for this study are the all-cause mortality rate, determined at Day 42 and Day 84 (Table 13), and the DRC assessed response to therapy at the EOT (Table 15). Overall mortality was 38% at Day 42, and 43% at Day 84. The primary treatment group mortality was similar to the overall rate, with 33% 42-day mortality and 43% 84-day mortality.

Table 13: All-Cause Mortality through Day 42 and Day 84 in the mITT Mucorales Population

Outcome	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
By Day 42				
All-Cause Mortality†	7 (33.3%)	5 (45.5%)	2 (40.0%)	14 (37.8%)
Deaths	7 (33.3%)	4 (36.4%)	2 (40.0%)	13 (35.1%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)
By Day 84				
All-Cause Mortality‡	9 (42.9%)	5 (45.5%)	2 (40.0%)	16 (43.2%)
Deaths	9 (42.9%)	4 (36.4%)	2 (40.0%)	15 (40.5%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)

Source: FDA reviewer generated from datasets from Study 9766-CL-0103

† A patient with a last known survival status before Day 42 was counted as dead.

‡ A patient with a last known survival status before Day 84 was counted as dead.

Subgroup analyses were performed on all-cause mortality through Day 42 for the risk factors of hematologic malignancy, diabetes, disseminated disease, CNS involvement and surgery/debridement (Table 14). All-cause mortality through Day 42 was highest for the risk factor of CNS involvement (66.7% of mITT-Mucorales overall, all of whom were primary therapy patients), though these results were based on a small number of patients with this risk factor. For group comparison to existing scientific literature, overall mortality in the hematologic malignancy group was 13/22 (59.1%) at 84 days.

Table 14: All-cause Mortality through Day 42 by Risk Factor and Therapy Status (mITT-Mucorales Population - Study 9766-CL-0103)

Risk Factor	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Hematologic malignancy	5/11 (45.5%)	5/7 (71.4%)	2/4 (50%)	12/22 (54.5%)
Diabetes	1/4 (25%)	0	0	1/4 (25%)
Disseminated disease	4/8 (50%)	1/2 (50.0%)	0/1	5/11 (45.5%)
CNS involvement	4/6 (66.7%)	0	0	4/6 (66.7%)
Surgery/debridement†	4/9 (44.4%)	1/1 (100%)	0	5/10 (50%)

mITT-Mucorales: ITT patients who had proven or probable invasive mucormycosis as determined by the DRC; A patient with an unknown survival status was counted as dead.
† Surgery was between 7 days before and 7 days after start of study drug.
Source: FDA reviewer generated from case reports from study 9766-CL-0103

The DRC assessed overall response rate at EOT in the mITT-Mucorales population (Table 15) was 31.4%, with 14.3% of patients assessed to be a complete success and 17.1% assessed to be a partial success. Approximately one third, 28.6% of patients, was assessed as stable. For primary therapy patients, 31.6% of patients were assessed to be a success, with 15.8% of patients assessed to be a complete and 15.8% a partial success.

Table 15: DRC Assessed Overall Response at EOT by Therapy Status (mITT-Mucorales Population - Study 9766-CL-0103)

Outcome Response	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Success	6/19 (31.6%)	4/11 (36.4%)	1/5 (20%)	11/35 (31.4%)
Complete	3/19 (15.8%)	2/11 (18.2%)	0	5/35 (14.3%)
Partial	3/19 (15.8%)	2/11 (18.2%)	1/5 (20%)	6/35 (17.1%)
Failure	13/19 (68.4%)	7/11 (63.6%)	4/5 (80%)	24/35 (68.6%)
Stable	6/19 (31.6%)	2/11 (18.2%)	2/5 (40%)	10/35 (28.6%)
Progression	7/19 (36.8%)	5/11 (45.5%)	2/5 (40%)	14/35 (40%)

Source: FDA reviewer generated from case reports from study 9766-CL-0103

DRC-determined success at the end of treatment accounts for patients who survived the study period with slowly progressing infections, as well as patients surviving on alternative antifungal therapy following study withdrawal. There were two patients in the latter category. Patient 0141-03 (refractory group) withdrew due to the adverse reaction of elevated liver chemistry tests on Day 33, received posaconazole, and survived beyond Day 84. He was deemed a stable response

(failure) at EOT. Patient 0115-14 (primary group) withdrew from study due to progression of underlying malignancy on day 33, and was treated with posaconazole until her death on Day 56. The DRC considered her overall response as stable (failure) at EOT.

8.2.4 Analysis of Secondary Endpoints(s)

The secondary efficacy outcomes included clinical, mycological and radiological response assessed by the DRC at Day 42, Day 84 and EOT. In addition, the DRC assessed the attribution of death to the IFD for death up to Day 42 and for death up to Day 84 as either directly due to consequences of progressive IFD, associated with the evidence of residual or ongoing IFD, associated with no evidence of residual or ongoing IFD, indeterminate cause or no known death.

The DRC assessments of success rates for clinical, mycological and radiological response at EOT were higher for clinical response (45.2%) than mycological (34.3%) and radiological (18.2%), for the mITT-Mucorales population (Table 16). For primary therapy patients, the DRC assessments of success rates for clinical, mycological and radiological response at EOT were 55.6%, 31.6% and 16.7% respectively.

Table 16: DRC Assessed Success Rates for Clinical, Mycological, and Radiological Response at EOT by Therapy Status (mITT-Mucorales Population - Study 9766-CL-0103)*

Outcome Response	Primary Therapy (n = 19)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 35)
Clinical Response				
Success	10/18 (55.6%)	2/9 (22.2%)	2/4 (50.0%)	14/31 (45.2%)
Failure	8/18 (44.4%)	7/9 (77.8%)	2/4 (50.0%)	17/31 (54.8%)
Not Determined	1	2	1	4
Mycological Response				
Success	6/19 (31.6%)	4/11 (36.4%)	2/5 (40.0%)	12/35 (34.3%)
Failure	13/19 (68.4%)	7/11 (63.6%)	3/5 (60.0%)	23/35 (65.7%)
Radiological Response				
Success	3/18 (16.7%)	2/10 (20.0%)	1/5 (20.0%)	6/33 (18.2%)
Failure	15/18 (83.3%)	8/10 (80.0%)	4/5 (80.0%)	27/33 (81.8%)
Not Determined	1	1	0	2

* Subjects who were still actively participating in the study at the interim cut of the database were not included in this analysis at the EOT time point.

Source: FDA reviewer generated from case reports from study 9766-CL-0103

Additional secondary endpoints include evaluations by the DRC at 42 and 84 days. These data points provide limited information. At 42 days, 21 of 37 subjects were evaluable because 16 fatalities were excluded. There was one success, with 16 patients deemed stable. Similarly, at 84 days, only 19 of 37 subjects were alive and evaluable. As such, DRC determinations at the EOT were more informative.

8.2.5 Analysis of Historical Control Populations

The Applicant provided a review of the scientific literature and matched controls within the European Fungiscope database to support the efficacy of isavuconazonium relative to amphotericin B deoxycholate. Amphotericin B is the only FDA-approved drug for invasive

mucormycosis. The Fungiscope matched case analysis provides limited evidence of isavuconazonium efficacy relative to amphotericin B because of the wide confidence margins and the absence of an agreed upon non-inferiority margin. We have therefore concentrated on the benefit of isavuconazonium relative to no treatment.

Natural History of Invasive Mucormycosis

We identified three epidemiologic reports that provide limited support for assigning a mortality rate of nearly 100% for untreated invasive mucormycosis. A paper by Roden and colleagues[7] indicated an overall mortality rate of 97% in a review of 929 reported cases, but many of the cases were identified post-mortem. We contacted the authors to ascertain the number of patients who were diagnosed with mucormycosis prior to death. There were 241 patients who received no treatment. Of these, 8 (3%) survived. Of the 233 patients that died, 18 (8%) were diagnosed pre-mortem and 215 (92%) were diagnosed post mortem.

We next reviewed a study by Skiada and colleagues[8], which indicated that 21 of 22 (95%) untreated patients did not survive. While only 10 cases (4%) were diagnosed post-mortem, information is lacking on how these cases were distributed among the treatment groups, the presence of underlying medical conditions, and the duration of the follow up from the time of diagnosis.

The publication most closely approximating a natural history study in a modern population was from Dimitrios Kontoyiannis' group (Chamilos *et al*)[9]. A total of 70 consecutive patients with hematologic malignancy and mucormycosis during the period of 1989–2006 were analyzed for 84 day mortality when amphotericin B–based therapy was delayed. The study used diagnostic criteria similar to Trial 9766-CL-0103. A delay of six days in initiating amphotericin B–based therapy resulted in a two-fold increase in mortality rate at 84 days after diagnosis (82.9%, 95% CI [68.9, 96.8], n = 35), compared with early treatment (48.6%). All patients were alive with an active infection at the time of diagnosis. The author's six-day cutoff was selected based upon a statistical analysis intended to define a clinically meaningful delay of treatment. The study indicated that mortality approached 100% at 84 days if left untreated, but did not present data for all 70 patients individually.

In the isavuconazonium-treated population, nine of 22 (41%, 95% CI [20.4, 61.5]) subjects with hematologic malignancy died by 84 days. Comparing the reported 82.9% 84-day mortality in the Chamilos *et al* study to the 41% in the isavuconazonium-treated group suggests a benefit of isavuconazonium treatment. As this represents the benefit of isavuconazonium treatment relative to a six day delay of treatment, it can be considered a conservative assessment of isavuconazonium treatment versus the absence of treatment.

The Applicant performed an audit of the Fungiscope database, an observational registry established in 2003. In this database, there are 136 cases of invasive mucormycosis with available survival data through Day 42, 29 of whom did not receive treatment and all 29 died. In

7 Roden, M.M., Zaoutis, T.E., Buchanan, W.L., Knudsen, T.A., Sarkisova, T.A., Schaufele, R.L., et al. "Epidemiology and outcome of zygomycosis: a review of 929 reported cases." Clin Infect Dis. 2005;41:634-53.

8 Skiada A., Pagano L., Groll A., *et al.* "Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007." Clin Microbiol Infect. 2011 Dec;17(12):1859-67.

9 Chamilos, G., Lewis, R.E., Kontoyiannis, D.P. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." Clin Infect Dis. 2008 Aug 15;47(4):503-9.

the untreated patients, most were diagnosed post-mortem or shortly before death, similar to the Roden and Skiada papers.

While the epidemiologic studies are limited, they represent the best available data. It is reasonable to believe that infection with invasive mucormycosis carries a very high risk of mortality, and the mortality rates quoted by the Skiada, Roden, and Fungiscope database may be reflective of the actual mortality rate if the infection is left untreated. There is no serologic biomarker for invasive mucormycosis, and patients with disease may go undiagnosed until autopsy. Post-mortem diagnosis is consistent with the rapid progression of this disease and the difficulty in diagnosis.

Table 17 provides a summary of the estimated mortality of untreated patients relative to amphotericin-treated patients.

Table 17: Mortality Rates and 95% CIs in Amphotericin-Treated, and Untreated Patients (All patients, including Post-Mortem Diagnosis) Patients

Study	Amphotericin-Treated Patients ACM (%) [95% CI][1]	Untreated Patients ACM (%) [95% CI][1]
Roden	244/648 (37.7%) [33.9, 41.5]	233/241 (96.7%) [93.6, 98.6]
Skiada	58/152 (38.2%) [30.4, 46.4]	21/22 (95.5%) [77.2, 99.9]
Fungiscope[2]	41/107 (38.3%) [29.1, 48.2]	29/29 (100%)[2] [88.1, 100.0]
Meta-Analysis[3]	37.8% [34.7, 41.0]	96.2% [94.0, 98.4]

1) Confidence intervals were calculated by exact binomial method; 95% CI from the meta-analysis was based on the normal approximation.
2) Day 42: 13 with pre-mortem diagnosis typically within a week of death plus post-mortem diagnosis
3) Based on Roden, Skiada, and Fungiscope. Number of Treated patients = 907. Number of Untreated patients = 292.
Source: Adapted from Applicant's Information Request Response Table 1, November 18, 2014.

The mortality rate and 95% confidence intervals for patients with proven or probable invasive mucormycosis from Study 9766-CL-0103 are presented in Table 18 in comparison to the mortality data from untreated patients. In this analysis, the upper limit of the 95% confidence interval for mortality in the isavuconazonium treatment group is below the lower limit of the 95% confidence interval for no treatment.

Table 18: Mortality Rates and 95% CIs in Isavuconazonium-Treated Patients and Untreated Patients

Timepoint	ISA Treated Patients All Mucor ACM[1] (%) [95% CI][2]	ISA Treated Patients Mucor Primary Therapy ACM (%) [95% CI][2]	6-day delay Chamilos et al. ACM (%) [95% CI][2]	Untreated Patients Mucor Meta-Analysis[3] ACM (%) [95% CI][2]
Day 42	14/37 (37.8%) [22.5, 55.2]	7/21 (33.3%) [14.6, 57.0]	82.9% [68.9, 96.8]	96.2% [94.0, 98.4]
Day 84	16/37 (43.2%) [27.1, 60.5]	9/21 (42.9%) [21.8, 66.0]		

1) 1 patient with unknown survival status at day 42 was assumed to be dead
2) Confidence intervals were calculated using exact binomial method
3) Based on Roden, Skiada, and Fungiscope. Number of Untreated patients = 292
Source: Adapted from Sponsor's Information Request Response Table 2, November 18, 2014.

Matched-case Analysis for Primary Therapy of Patients with Invasive Mucormycosis

The Applicant performed an additional analysis to compare isavuconazonium primary therapy with the current standard of care, amphotericin B based therapy. Trial subjects with primary, proven or probable mucormycosis were matched with patients from the Fungiscope Registry Database who received primary therapy with amphotericin B for proven or probable invasive mucormycosis. The Fungiscope Registry is a global web-based database, coordinated from the Clinical Trials Centre at the University of Cologne, Germany. It contains a collection of information on rare fungal infections, including more than 150 cases of invasive mucormycosis diagnosed and treated between 2003 and 2013.

Patients from Study 9766-CL-0103 were matched with up to three controls from the Fungiscope Registry Database for a total of 33 patients in the control group. Case matching used three primary criteria:

- Severe disease, defined as CNS involvement or disseminated disease, with the latter defined as a disease involving more than 1 non-contiguous organ.
- Surgery intended as therapeutic intervention for invasive mucormycosis and defined as resection/debridement at the site of infection 7 days prior to or after the start of their primary treatment.
- Underlying condition of hematologic malignancy.

The all-cause mortality through Day 42 is presented in Table 19.

Table 19: Observed All-Cause Mortality Comparing Trial 9766-CL-0103 to the Matched Fungiscope Controls

	All-cause Mortality	95% CI	Width of 95% CI
Observed Mortality - Trial 0103 Primary Therapy Cases	33.3% (7/21)	(14.6%, 57.0%)	42%
Observed Mortality - Fungiscope Matched-Controls	39.4% (13/33)	(22.9%, 57.9%)	35%

Source: Adapted from Application Module 5 Fungiscope Matched-Case Control Study and Applicant's Information Request Response November 18, 2014.

9 CLINICAL SAFETY

9.1 Summary

Isavuconazonium demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparator, voriconazole. The proportion of all known patient deaths was similar between treatment groups (ISA: 31.5%, 81/257; VRC: 33.6%, 87/259). More than half of the subjects experienced a treatment emergent serious adverse reaction (SAR) in either treatment group. The overall incidence of treatment emergent SAR was slightly lower in the isavuconazonium-treated subjects, 134/257 (52.1%), than in the voriconazole-treated subjects, 149/259 (57.5%). There were fewer adverse reactions leading to discontinuation of therapy in the isavuconazonium treatment arm. The incidence of treatment emergent adverse effects (TEAE) in isavuconazonium-treated subjects was lower than voriconazole-treated subjects for the hepatobiliary, eye, and skin system organ classes (SOC).

The major safety findings are consistent with the known adverse effects characteristic of azole-class antifungal drugs, namely hepatotoxicity, drug-induced liver injury, hypersensitivity

reactions, and infusion-related reactions. One unique safety finding relative to the other azole class antifungal drugs is exposure-related shortening of the QT interval, the clinical significance of which is uncertain.

9.2 Methods

The safety population included all subjects who received at least one dose of study drug. The safety review primarily focuses on Trial 9766-CL-0104, as this was a randomized, controlled study design for the intended indication of invasive aspergillosis. Safety analyses were also conducted using the integrated dataset of all four phase 2 and 3 trials. Adverse reactions from phase 1 trials were also evaluated.

Standard safety evaluations were conducted in all trials and included physical examinations, vital signs, and clinical laboratory evaluations, as well as monitoring for AEs and concomitant medication usage. Comprehensive electrocardiogram (ECG) evaluations were conducted in two thorough QT studies.

9.3 Exposure

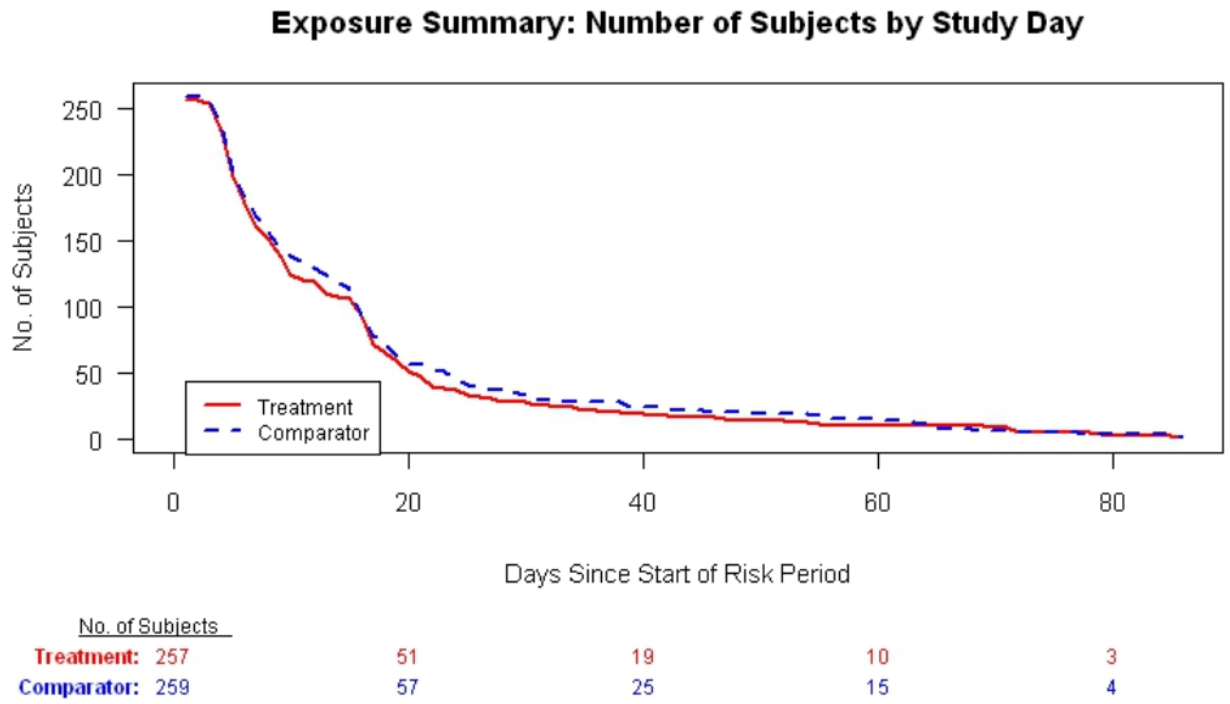
The safety population of 1692 subjects (Table 20), includes 1049 healthy subjects dosed in 38 integrated phase 1 trials, 144 subjects in the phase 2 population, and 403 subjects in the phase 3 trials. Subjects in the safety population are categorized by the treatment they received, irrespective of the treatment group to which they were randomized.

Table 20: Summary of Safety Populations in the Isavuconazonium Clinical Development Program

	Design	**Isavuconazonium (n)**	**Comparators/ Controls (n)**
Integrated phase 2 and 3 trials		**547**	**297**
Phase 2 trials		**144**	**38**
9766-CL-0101/WSA-CS-001	Double-blind	121	38
9766-CL-0102/WSA-CS-002	Open Label	23	0
Phase 3 trials		**403**	**259**
9766-CL-0103/WSA-CS-003	Open Label	146	0
9766-CL-0104/WSA-CS-004	Double-blind	257	259
Integrated phase 1 trials	Open Label	**1001**	**177**
Phase 1 trials completed after the data cutoff date	Open Label	**144**	**0**
Renally-impaired subjects	Open Label	24	0
Hepatically-impaired subjects	Open Label	64	0
TOTAL		**1692**	**474**

Within the Phase 3 controlled study population (trial 9766-CL-0104), the relative exposure to study drug and comparator are similar, as depicted in Figure 5.

Figure 5: Exposure: Trial 9766-CL-0104 to Isavuconazonium (Treatment) and Voriconazole (Comparator)



Source: FDA Reviewer generated using Empirica Study 3.1 with combined SDTM datasets from Study 9766-CL-0104

The phase 3 trials utilized the same dosing regimen for isavuconazonium, however, Trial 9766-CL-0103 allowed for extended treatment beyond 84 days. The Phase 2 trials utilized multiple dosing regimens, ranging from 50 mg/day to 400 mg/day maintenance from 21 days to 28 days. A summary of the overall isavuconazonium exposure is provided in Table 21.

Table 21: Summary of Isavuconazonium Exposure in the Phase 2 and 3 Trials (Safety Analysis Set)

Characteristic	Phase 2 (n = 144)	Phase 3 (n = 403)	Total (n = 547)
Total Duration (days)			
Mean (SD)	14.8 (4.58)	76.1 (91.16)	59.9 (82.78)
Median	14.0	57.0	28.0
Min - Max	1 - 28	1 - 882	1 - 882
Total Duration Category (days)			
≤ 2	4 (2.8%)	9 (2.2%)	13 (2.4%)
> 2 to ≤ 7	3 (2.1%)	44 (10.9%)	47 (8.6%)
> 7 to ≤ 14	113 (78.5%)	35 (8.7%)	148 (27.1%)
> 14 to ≤ 21	15 (10.4%)	29 (7.2%)	44 (8.0%)
> 21 to ≤ 28	9 (6.3%)	18 (4.5%)	27 (4.9%)
> 28 to ≤ 42	0	33 (8.2%)	33 (6.0%)
> 42 to ≤ 56	0	33 (8.2%)	33 (6.0%)
> 56 to ≤ 84	0	97 (24.1%)	97 (17.7%)
> 84 to ≤ 126	0	38 (9.4%)	38 (6.9%)
> 126 to ≤ 180	0	33 (8.2%)	33 (6.0%)
> 180	0	34 (8.4%)	34 (6.2%)
Subject-years of Exposure (Total)	5.84	83.91	89.75

Source: Modified from Applicant Summary of Clinical Safety, Table 3.1

The highest dose of isavuconazonium administered to healthy subjects in phase 1 was 600 mg per day in a thorough QT study (9766-CL-0017). The highest dose of isavuconazonium

administered to patients in a phase 2 clinical trial was a 24-hour loading dose of 1600 mg of isavuconazonium followed by 800 mg on day 2 and 400 mg per day thereafter (9766-CL-0102).

In the phase 1 studies completed after the data cut-off date for inclusion in the integrated Phase 1 Population, 11 subjects with end-stage renal disease received two doses of isavuconazonium 200 mg and 21 subjects with various degrees of renal impairment received a single 200-mg dose of isavuconazonium. A total of 64 subjects with mild to moderate hepatic impairment received a single 100-mg dose of isavuconazonium.

9.4 Major Safety Results

9.4.1 Deaths

The proportion of all known patient deaths was similar between treatment groups (ISA: 31.5%, 81/257; VRC: 33.6%, 87/259). All known deaths include all patient deaths regardless of the number of days after the last dose of study drug. All known deaths also include patient deaths during the course of the study due to an adverse reaction (AR) that started prior to the first dose of study drug. Deaths that occurred following drug exposure, up to 28 days from the day of the last drug exposure, are considered treatment emergent adverse effects (TEAE). A summary of the categories of all known deaths that occurred in this study is found below, in Table 22.

Table 22: Categorization of Deaths Occurring within the Phase 3 Controlled Population

Category	ISA (n = 257)	VRC (n = 259)
Deaths within 28 days after EOT, TEAE reported	61	69
Deaths within 28 days after the EOT, AE reported (AE onset prior to treatment)	1	1
Deaths > 28 days after the EOT, TEAE reported	1	3
Deaths > 28 days after the EOT, AE reported	13	11
Deaths > 28 days after the EOT, no AE reported	5	3
Total of all known deaths following drug exposure	81	87

AE: adverse event; EOT: end of treatment; ISA: isavuconazonium; TEAE: treatment-emergent AE; VRC: voriconazole.
Source: FDA Reviewer generated using datasets from Study 9766-CL-0104

Treatment Emergent Adverse Events Leading to Death

The overall pattern of TEAEs leading to death was similar between treatment groups (ISA: 24.1%, 62/257; VRC: 27.8%, 72/259), and are summarized in Table 23. The TEAEs leading to death that occurred in ≥ 2% of patients in the isavuconazonium or voriconazole groups, respectively, were septic shock (3.1% vs 1.5%), sepsis (2.7% vs 1.9%), respiratory failure (2.3% vs 2.3%), acute myeloid leukemia (1.2% vs 2.7%) and multi-organ failure (0.4% vs 2.3%).

Table 23: Treatment Emergent Adverse Events Leading to Death in the Phase 3 Controlled Population

MedDRA v12.1 **System Organ Class** **Preferred Term**	**Isavuconazonium**	**Voriconazole**
Overall	**62 (24.1%)**	**72 (27.8%)**
Blood and lymphatic system disorders	**2 (0.8%)**	**1 (0.4%)**
Hemorrhagic disorder	1 (0.4%)	0
Pancytopenia	0	1 (0.4%)
Thrombocytopenia	1 (0.4%)	0
Cardiac disorders	**4 (1.6%)**	**5 (1.9%)**
Acute myocardial infarction	0	1 (0.4%)
Cardiac arrest	1 (0.4%)	3 (1.2%)
Cardio-respiratory arrest	1 (0.4%)	1 (0.4%)
Congestive cardiomyopathy	1 (0.4%)	0
Pericarditis	1 (0.4%)	0
Gastrointestinal disorders	**0**	**1 (0.4%)**
Rectal hemorrhage	0	1 (0.4%)
General disorders and administration site conditions	**2 (0.8%)**	**8 (3.1%)**
Death	1 (0.4%)	1 (0.4%)
Multi-organ failure	1 (0.4%)	6 (2.3%)
Sudden cardiac death	0	1 (0.4%)
Hepatobiliary disorders	**1 (0.4%)**	**0**
Hepatitis acute	1 (0.4%)	0
Immune system disorders	**1 (0.4%)**	**0**
Acute graft versus host disease	1 (0.4%)	0
Infections and infestations	**28 (10.9%)**	**18 (6.9%)**
Acinetobacter bacteremia	1 (0.4%)	0
Aspergillosis	3 (1.2%)	2 (0.8%)
Bronchopulmonary aspergillosis	1 (0.4%)	0
Endocarditis	1 (0.4%)	0
Fungal infection	3 (1.2%)	2 (0.8%)
Fusarium infection	1 (0.4%)	0
Infection	1 (0.4%)	0
Klebsiella sepsis	0	1 (0.4%)
Mucormycosis	1 (0.4%)	0
Pneumonia	1 (0.4%)	2 (0.8%)
Pseudomonal bacteremia	0	1 (0.4%)
Pseudomonal sepsis	0	1 (0.4%)
Sepsis	7 (2.7%)	5 (1.9%)
Septic shock	8 (3.1%)	4 (1.5%)
Stenotrophomonas sepsis	0	1 (0.4%)
Metabolism and nutrition disorders	**0**	**2 (0.8%)**
Hypoglycemia	0	1 (0.4%)
Metabolic acidosis	0	1 (0.4%)
Neoplasms benign, malignant and unspecified	**10 (3.9%)**	**21 (8.1%)**
Acute lymphocytic leukemia recurrent	0	1 (0.4%)
Acute myeloid leukemia	3 (1.2%)	7 (2.7%)
Acute myeloid leukemia recurrent	0	4 (1.5%)
B-cell lymphoma	0	1 (0.4%)
Blast cell crisis	1 (0.4%)	1 (0.4%)
Burkitt's leukemia	0	1 (0.4%)
Chronic lymphocytic leukemia	0	2 (0.8%)
Chronic lymphocytic leukemia recurrent	1 (0.4%)	0
Lymphoma	0	1 (0.4%)

Malignant neoplasm progression	1 (0.4%)	1 (0.4%)
Multiple myeloma	2 (0.8%)	0
Myelodysplastic syndrome	1 (0.4%)	0
Myeloid leukemia	1 (0.4%)	1 (0.4%)
Neoplasm progression	0	1 (0.4%)
Nervous system disorders	**3 (1.2%)**	**7 (2.7%)**
Cerebral hemorrhage	0	1 (0.4%)
Encephalitis	0	1 (0.4%)
Hemorrhage intracranial	2 (0.8%)	3 (1.2%)
Neurotoxicity	1 (0.4%)	0
Stupor	0	1 (0.4%)
Subarachnoid hemorrhage	0	1 (0.4%)
Renal and urinary disorders	**1 (0.4%)**	**0**
Renal failure	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	**14 (5.4%)**	**12 (4.6%)**
Acute respiratory distress syndrome	0	1 (0.4%)
Acute respiratory failure	3 (1.2%)	1 (0.4%)
Hemoptysis	2 (0.8%)	1 (0.4%)
Pulmonary embolism	0	1 (0.4%)
Pulmonary hemorrhage	2 (0.8%)	1 (0.4%)
Pulmonary hypertension	0	1 (0.4%)
Respiratory distress	1 (0.4%)	0
Respiratory failure	6 (2.3%)	6 (2.3%)
Vascular disorders	**2 (0.8%)**	**1 (0.4%)**
Deep vein thrombosis	0	1 (0.4%)
Hemorrhage	1 (0.4%)	0
Hypovolemic shock	1 (0.4%)	0

Source: FDA Reviewer generated using datasets from Trial 9766-CL-0104

Given that the ITT population contains immunosuppressed subjects with malignancy, significant mortality due to progression of infections and malignancy is not unexpected.

There were three patient deaths (South Africa) in the Phase 2 safety population (n=144), all related to progression of tuberculosis. There were no deaths in the Phase 1 population.

9.4.2 Nonfatal Serious Adverse Events and Common Adverse Events

Within the Phase 3 controlled trial population, more than half of the subjects experienced a treatment emergent serious adverse event (SAE) in either treatment group. The overall incidence was lower in the isavuconazonium-treated subjects, 134/257 (52.1%), than in the voriconazole-treated subjects 149/259 (57.5%). After excluding the subjects with a fatal outcome, 99/257 (38.5%) of isavuconazonium-treated subjects and 121/259 (46.7%) of voriconazole-treated subjects experienced a treatment emergent SAE. The incidence of nonfatal, treatment emergent, SAE by SOC is categorized in Table 24. The categories for which isavuconazonium had a higher incidence than voriconazole of treatment emergent SAE are expanded to the lowest level term. A TEAE with a missing seriousness value was considered a serious TEAE.

Table 24: Nonfatal Serious Treatment Emergent Adverse Events by System Organ Class in the Phase 3 Controlled Population

	Isavuconazonium (n = 257)		**Voriconazole (n = 259)**	
MedDRA v12.1 System Organ Class Preferred Term	**Number of Subjects**	**Proportion (%)**	**Number of Subjects**	**Proportion (%)**
Overall	**99**	**38.5**	**121**	**46.7**
Blood and lymphatic system disorders	27	10.5	17	6.6

Agranulocytosis	2	0.8	0	0.0
Anemia	1	0.4	2	0.8
Febrile neutropenia	14	5.4	5	1.9
Hemorrhagic anemia	0	0.0	1	0.4
Leukocytosis	1	0.4	0	0.0
Microangiopathic hemolytic anemia	0	0.0	1	0.4
Neutropenia	4	1.6	3	1.2
Pancytopenia	4	1.6	3	1.2
Splenic infarction	1	0.4	0	0.0
Thrombocytopenia	2	0.8	4	1.5
Thrombocytopenic purpura	0	0.0	1	0.4
Respiratory, thoracic and mediastinal disorders	27	10.5	33	12.7
Infections and infestations	26	10.1	46	17.8
Nervous system disorders	14	5.5	10	3.9
Aphasia	0	0.0	1	0.4
Brain stem stroke	1	0.4	0	0.0
Central nervous system lesion	1	0.4	1	0.4
Cerebral ischemia	1	0.4	0	0.0
Convulsion	3	1.2	1	0.4
Dizziness	0	0.0	1	0.4
Encephalopathy	1	0.4	1	0.4
Epilepsy	2	0.8	1	0.4
Febrile convulsion	1	0.4	0	0.0
Grand mal convulsion	0	0.0	1	0.4
Headache	1	0.4	0	0.0
Hemiplegia	0	0.0	1	0.4
Ischemic stroke	1	0.4	1	0.4
Paraplegia	1	0.4	1	0.4
Polyneuropathy	2	0.8	0	0.0
Tremor	0	0.0	1	0.4
7th nerve paralysis	0	0.0	1	0.4
General disorders and administration site conditions	10	3.9	12	4.6
Gastrointestinal disorders	9	3.5	11	4.3
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9	3.5	9	3.5
Renal and urinary disorders	9	3.5	10	3.9
Cardiac disorders	7	2.7	7	2.7
Immune system disorders	3	1.2	6	2.3
Injury, poisoning and procedural complications	3	1.2	3	1.2
Investigations	3	1.2	6	2.3
Musculoskeletal and connective tissue disorders	3	1.2	0	0.0
Skin and subcutaneous tissue disorders	3	1.2	2	0.8
Decubitus Ulcer	1	0.4	0	0.0
Dermatitis	1	0.4	0	0.0
Panniculitis	1	0.4	0	0.0
Rash	0	0.0	2	0.8
Eye disorders	2	0.8	1	0.4
Hepatobiliary disorders	2	0.8	6	2.3
Metabolism and nutrition disorders	2	0.8	6	2.3
Vascular disorders	2	0.8	5	1.9
Psychiatric disorders	1	0.4	6	2.3

Source: Reviewer generated using JMP 11 and ADAE dataset from trial 9766-CL-0104

*Individual subjects may have several closely related nonfatal SAE (i.e. WSAC004-3301-11 voriconazole arm: aphasia, hemiplegia and 7th nerve palsy)

The high incidence of SAEs within the blood and lymphatic system disorders SOC is expected, as 23 of 27 isavuconazonium-treated subjects and 14 of the 17 voriconazole-treated subjects had an uncontrolled hematologic malignancy at baseline. An examination of the nervous system disorders SOC in Table 24 at the lowest level term reveals more serious, non-fatal convulsive AEs (convulsion, epilepsy, febrile convulsion, and grand mal convulsion) within the isavuconazonium treatment arm when combining these preferred terms, (7 events in 6 subjects) than within the voriconazole arm (three events in three subjects). The cases were confounded by underlying conditions and/or exposure to concomitant medications with seizure potential. Convulsions are described for other systemic antifungal azoles, such as fluconazole[10], which also contains a precaution on the label advising against operating a vehicle due to dizziness or seizure.[11]

Table 25: Serious Treatment Emergent Adverse Events (≥ 1% in Either Treatment Group)

MedDRA v12.1 Preferred Term	**Isavuconazonium (n = 257)**	**Voriconazole (n = 259)**
Overall	**134 (52.1%)**	**149 (57.5%)**
Respiratory failure	14 (5.4%)	12 (4.6%)
Septic shock	14 (5.4%)	10 (3.9%)
Febrile neutropenia	14 (5.4%)	5 (1.9%)
Pyrexia	8 (3.1%)	10 (3.9%)
Sepsis	7 (2.7%)	8 (3.1%)
Renal failure acute	6 (2.3%)	8 (3.1%)
Pneumonia	5 (1.9%)	10 (3.9%)
Acute respiratory failure	5 (1.9%)	5 (1.9%)
Dyspnea	5 (1.9%)	1 (0.4%)
Aspergillosis	4 (1.6%)	3 (1.2%)
Neutropenia	4 (1.6%)	3 (1.2%)
Pancytopenia	4 (1.6%)	3 (1.2%)
Respiratory distress	4 (1.6%)	3 (1.2%)
Acute myeloid leukemia	3 (1.2%)	8 (3.1%)
Thrombocytopenia	3 (1.2%)	4 (1.5%)
Fungal infection	3 (1.2%)	3 (1.2%)
Renal failure	3 (1.2%)	2 (0.8%)
Convulsion	3 (1.2%)	1 (0.4%)
Hemorrhage intracranial	2 (0.8%)	3 (1.2%)
Multi-organ failure	1 (0.4%)	7 (2.7%)
Cardiac arrest	1 (0.4%)	5 (1.9%)
Gastrointestinal hemorrhage	0	3 (1.2%)
Bacterial sepsis	0	4 (1.5%)
Staphylococcal bacteremia	0	3 (1.2%)
Acute myeloid leukemia recurrent	0	5 (1.9%)
Epistaxis	0	4 (1.5%)
Lung infiltration	0	3 (1.2%)
Pulmonary embolism	0	3 (1.2%)

When all SAEs are tabulated by frequency at the preferred term level (Table 25), the number of patients who experienced serious TEAEs remained generally similar between treatment groups with the exception of febrile neutropenia (5.4% vs 1.9%), septic shock (5.4% vs 3.9%) and

[10] Matsumoto, K., Ueno, K., Yoshimura, et al. "Fluconazole-induced convulsions at serum trough concentrations of approximately 80 µg/mL". *Ther Drug Monit.* 2000 Oct;22(5):635-6.
[11] http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019949s060,020090s044lbl.pdf

dyspnea (1.9% vs 0.4%), which were more often experienced by isavuconazonium- treated patients. Hallucination and visual hallucination, were experienced by voriconazole-treated, but not by isavuconazonium-treated patients.

9.5 Adverse Events Leading to Study Drug Discontinuation

There were fewer isavuconazonium patients (14.4%) than voriconazole patients (22.8%) with at least one adverse event leading to permanent discontinuation of study drug. Patients in the isavuconazonium group compared to the voriconazole group had fewer events in the hepatobiliary disorders (0.4% vs 2.3%), skin and subcutaneous tissue disorders (0.8% vs 1.9%) and psychiatric disorders (0.8% vs 2.3%) SOCs leading to discontinuation of study drug. The proportion of patients was similar between treatment groups for the remaining SOCs. The most common TEAEs leading to study drug discontinuation that were reported in ≥ 1.0% of either the isavuconazonium or voriconazole treatment groups, respectively, were respiratory failure (0.8%, 2 patients vs 1.5%, 4 patients), sepsis (0.4%, 1 patient vs 1.2%, 3 patients), and acute myeloid leukemia (0 patients vs 1.5%, 4 patients), rash (0 patients vs 1.5%, 4 patients), bacterial sepsis (0 patients vs 1.2%, 3 patients) and visual hallucination (0 patients vs 1.2%, 3 patients).

In the phase 1 healthy volunteer population, seven discontinuations occurred in the group of 39 subjects taking multiple doses of 600 mg isavuconazonium. Reasons for discontinuation included AEs of anxiety (3/39), flushing (3/39), headache (3/39), dizziness (2/39) attention disturbances (2/39), nausea (2/39), diarrhea (1/39), and vomiting (1/39).

9.6 Common Adverse Events

In the Phase 3 Controlled Population, one or more TEAEs were reported by 96.1% of isavuconazonium-treated patients and 98.5% of voriconazole-treated patients. The most common adverse reactions reported with isavuconazonium treatment were nausea, vomiting and diarrhea. Significant differences were observed for isavuconazonium vs. voriconazole for the following SOCs: hepatobiliary disorders (8.9% v 16.2%), eye disorders (15.2% vs 26.6%), skin disorders (33.5% vs 42.5%), psychiatric disorders (27.2% vs 33.2%), and cardiac disorders (16.7% vs 22.0%). Within these SOCs, the differences between groups are likely related to known adverse effect of voriconazole (e.g., visual disturbances and exfoliative rash).

In the Phase 3 Controlled Population, the more common adverse events (occurring with an incidence ≥ 5%) in either the isavuconazonium or voriconazole treatment groups are shown in Table 26.

Table 26: Treatment Emergent Adverse Events in ≥ 10% of Patients in Either Treatment Group

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	**247 (96.1%)**	**255 (98.5%)**
Nausea	71 (27.6%)	78 (30.1%)
Vomiting	64 (24.9%)	73 (28.2%)
Diarrhea	61 (23.7%)	60 (23.2%)
Pyrexia	57 (22.2%)	78 (30.1%)
Hypokalemia	45 (17.5%)	56 (21.6%)
Headache	41 (16.0%)	38 (14.7%)
Constipation	36 (14.0%)	54 (20.8%)
Dyspnea	34 (13.2%)	29 (11.2%)
Cough	33 (12.8%)	35 (13.5%)

Febrile neutropenia	32 (12.5%)	38 (14.7%)
Chills	27 (10.5%)	23 (8.9%)
Fatigue	27 (10.5%)	18 (6.9%)
Edema peripheral	26 (10.1%)	31 (12.0%)
Back pain	26 (10.1%)	19 (7.3%)
Abdominal pain	25 (9.7%)	36 (13.9%)
Hypertension	25 (9.7%)	31 (12.0%)
Decreased appetite	22 (8.6%)	28 (10.8%)
Epistaxis	21 (8.2%)	28 (10.8%)
Hypotension	21 (8.2%)	28 (10.8%)
Rash	17 (6.6%)	28 (10.8%)
Hypomagnesemia	14 (5.4%)	27 (10.4%)

Source: FDA Reviewer generated using datasets from Trial 9766-CL-0104

Within the phase 1 multiple dose groups, the highest incidence of TEAEs occurred in the 600 mg group (34/39, 87.2%). TEAEs in the 600 mg group that occurred at a higher rate than that seen in the other multiple dose groups included flushing (20/39, 51.3%), nausea (10/39, 25.6%), anxiety (5/39, 12.8%), paresthesia (6/39, 15.4%), dry mouth (5/39, 12.8%), dysgeusia (4/39, 10.3%), oral hypoesthesia (4/39, 10.3%), disturbance in attention (4/39, 10.3%), palpitations (4/39, 10.3%), vomiting (3/39, 7.7%), and oral paresthesia (2/39, 5.1%).

9.7 Submission Specific Safety Concerns

9.7.1 Hepatotoxicity and Elevated Liver Test Results

Hepatic TEAEs by severity and outcome in the phase 3, controlled trial population, are listed in Table 27. No hepatic TEAEs were reported among isavuconazonium-treated subjects in the phase 1 population.

Table 27: Hepatobiliary TEAEs by Severity and Outcome

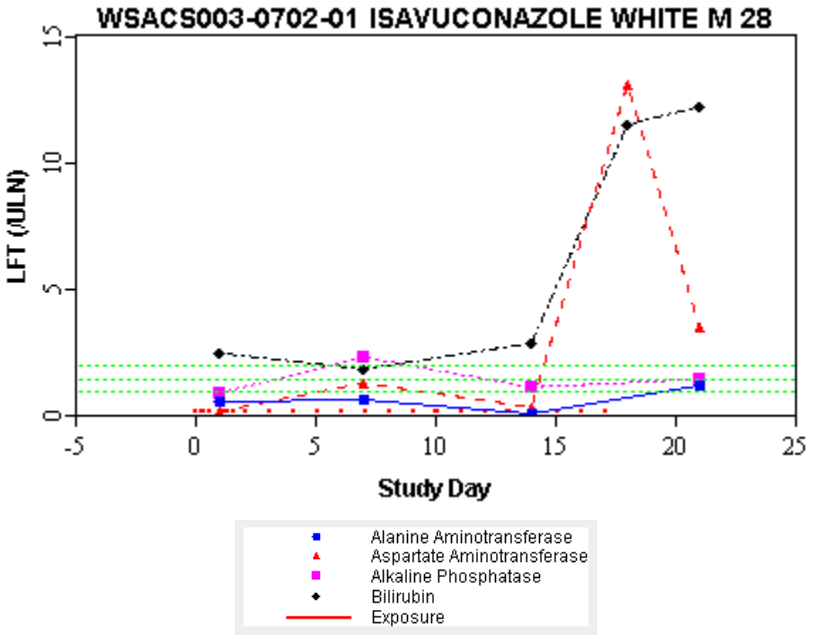
	Phase 3 Controlled Trial	
	Isavuconazonium (n = 257)	**Voriconazole (n = 259)**
Any TEAE	**23 (8.9%)**	**42 (16.2%)**
Mild*	6 (2.3%)	14 (5.4%)
Moderate*	12 (4.7%)	16 (6.2%)
Severe*	5 (1.9%)	12 (4.6%)
Serious TEAEs	**3 (1.2%)**	**6 (2.3%)**
TEAEs Leading to Discontinuation	**1 (0.4%)**	**6 (2.3%)**
TEAEs Leading to Death	**1 (0.4%)**	**0**

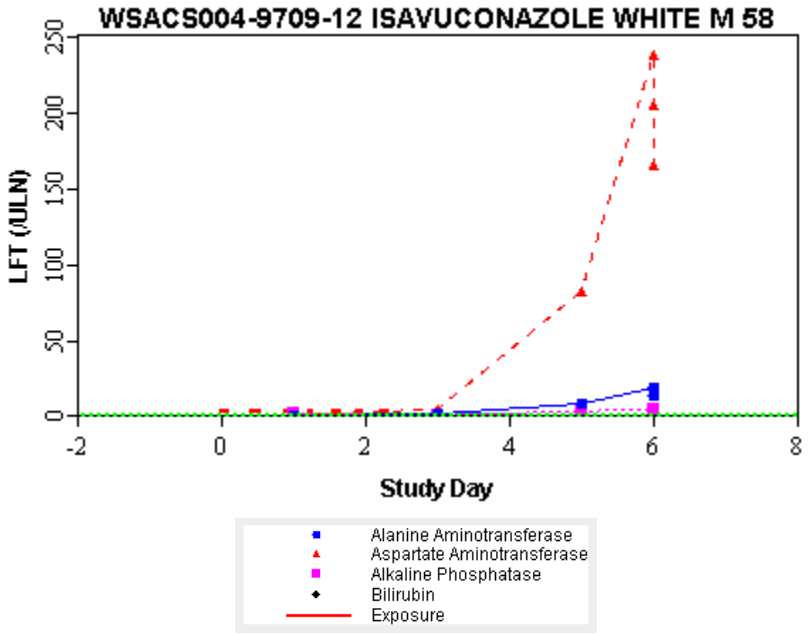
*Investigator Assessment

Source: Reviewer generated using JMP 11 and ADAE dataset from Trial 9766-CL-0104

In the combined Phase 2 and 3 Population, eight serious TEAEs in the hepatobiliary disorders SOC were reported with the following preferred terms (PTs): two patients with cholecystitis, and one patient each with cholangitis, cholelithiasis, liver disorder, acute hepatic failure, hepatitis, and acute hepatitis. Within the phase 3 controlled population, the three SAEs were hepatitis, acute hepatitis, and cholecystitis. A patient (Subject 9709-12) treated with isavuconazonium experienced acute hepatitis with a fatal outcome without a clear alternative etiology. A second patient (Subject 0702-01) had a suspected drug-related hepatic adverse reaction of acute hepatic failure, also resulting in a fatal outcome but a number of alternative etiologies were possible. Both patients are detailed in Table 28.

Table 28: Description of Selected Phase 3 Isavuconazonium-Treated Subjects with Serious Hepatic TEAEs

Study	Subject No.	Preferred Term	Comments
9766-CL-0103	0702-01	Acute hepatic failure	28 year old White male with history of chronic hepatitis C, AML s/p BMT day 223 c/b GVHD. Isavuconazonium discontinued day 18 due to acute hepatic failure, and patient died from multi-organ failure 5 days later with ongoing hepatic failure. Possible etiologies include activation of chronic hepatitis C, sepsis, AML progression, GVHD, and drug toxicity (isavuconazonium, haloperidol, meropenem, quetiapine, and/or oliclinomel). Patient had ALT or AST > 3xULN and ALP < 2xULN and T-Bili > 2xULN within 3 days apart, thus satisfying laboratory criteria for Hy's Law.  Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0103
9766-CL-0104	9709-12	Acute Hepatitis	58 year old White male with a history of large B-cell lymphoma, chronic lymphocytic leukemia, and unstaged SCC of the lung, being treated for *Aspergillus fumigatus* pneumonia. Drug discontinued Day 4 due to acute hepatitis (reported Day 5). Days 5-6 ALT and AST rose above 5x ULN. Subject died on Day 6 due to septic shock per investigator. Blood cultures were not positive, and hepatitis serology was not available. Autopsy was not performed. Concomitant medications include acetaminophen. The subject did not have bilirubin values reported, and as such, was not included in the list of subjects that satisfied laboratory criteria for Hy's Law.



Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0104

In the controlled phase 3 trial, there were a total of 24 hepatobiliary adverse events in the isavuconazonium treatment group for the entire study period. Of these events, 12 (50%) resolved, two (8%) were improving, nine (38%) were not resolved, and one (4%) event proved fatal (acute hepatitis). This is in comparison to voriconazole, in which there were 44 events: 21 (48%) resolved, 21 (48%) were not resolved, and two (4%) were recovering. Isavuconazonium therapy was discontinued in the one patient (Subject 9709-12) with fatal hepatitis, so reversibility, as well as re-challenge data, are not available.

Hy's Law

Elevated transaminases, either ALT or AST, two times above the upper limit of normal occurred in 16% of isavuconazonium-treated patients, and 19% of voriconazole-treated patients in the phase 3 controlled population. More substantial liver injury is associated with impaired hepatic elimination of bilirubin in the absence of cholestasis. Often referred to as Hy's Law[12], the laboratory criteria (combined ALT or AST > 3 x ULN and ALP < 2 x ULN and total bilirubin > 2 x ULN) were met in three isavuconazonium-treated patients and seven voriconazole-treated patients, consistent with the known hepatotoxicity of systemic triazoles.[13] Table 29 describes the incidence of post-baseline liver test elevations, specifically ALT, AST, ALP, and total bilirubin.

[12] Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

[13] Dolton, M.J., McLachlan, A.J. "Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity." Int J Antimicrob Agents. 2014 Sep;44(3):183-93.

Table 29: Assessment of Hepatotoxicity in the Phase 3 Controlled Population

		Isavuconazonium	Voriconazole
ALT	> 3 x ULN	31/249 (12.4%)	35/255 (13.7%)
	> 5 x ULN	17/249 (6.8%)	18/255 (7.1%)
	> 10 x ULN	5/249 (2.0%)	12/255 (4.7%)
	> 20 x ULN	1/249 (0.4%)	3/255 (1.2%)
AST	> 3 x ULN	24/249 (9.6%)	39/255 (15.3%)
	> 5 x ULN	13/249 (5.2%)	19/255 (7.5%)
	> 10 x ULN	4/249 (1.6%)	8/255 (3.1%)
	> 20 x ULN	3/249 (1.2%)	4/255 (1.6%)
ALT or AST	> 3 x ULN	39/250 (15.6%)	48/255 (18.8%)
	> 5 x ULN	21/250 (8.4%)	27/255 (10.6%)
	> 10 x ULN	6/250 (2.4%)	14/255 (5.5%)
	> 20 x ULN	4/250 (1.6%)	5/255 (2.0%)
ALP	> 1.5 x ULN	73/249 (29.3%)	98/254 (38.6%)
	> 3 x ULN	24/249 (9.6%)	34/254 (13.4%)
Total Bilirubin	> 2 x ULN	28/249 (11.2%)	23/255 (9.0%)
(ALT or AST) and Total Bilirubin	(ALT or AST) > 3 x ULN and Total Bilirubin > 1.5 x ULN	12/251 (4.8%)	14/255 (5.5%)
	(ALT or AST) > 3 x ULN and Total Bilirubin > 2 x ULN	8/251 (3.2%)	10/255 (3.9%)
(ALT or AST) and ALP and Total Bilirubin	(ALT or AST) > 3 x ULN and ALP < 2 x ULN and Total Bilirubin > 2 x ULN	3/251 (1.2%)	7/255 (2.7%)

Baseline, pre-exposure lab values in comparison to maximum values from initial drug exposure to 10 days after last dose of study drug.
Source: Modified from 9766-CL-0104 Clinical Study Report End-of-Text Tables 12.6.2.4.1 and 12.6.2.4.2

Within the combined phase 2 and phase 3 safety population, an additional two patients within Trial 9766-CL-0103 satisfied the laboratory criteria of Hy's Law, for a total of five isavuconazonium-treated patients 5/535 (0.9%) with ALT or AST > 3xULN and ALP < 2xULN and total bilirubin > 2xULN within three days apart. All of these cases reported alternative etiologies such as concurrent sepsis, multi-organ failure, concurrent use of hepatotoxic drugs, and/or improvement of hepatic enzyme elevations despite continued isavuconazonium treatment. Isavuconazonium is temporally related in each case and the contribution of the isavuconazonium to liver injury cannot be excluded.

9.7.2 Particulates in the IV Formulation

Following reconstitution, the intravenous isavuconazonium formulation may spontaneously hydrolyze in aqueous solution and precipitate as insoluble isavuconazole. As a result, the study drug was administered through an inline filter to remove particulates. Twenty-one patients in Study 9766-CL-0104 and six patients in Study 9766-CL-0103 were inadvertently administered intravenous isavuconazonium without an in-line filter. There were no embolic or thromboembolic AEs observed within this patient subpopulation. The overall phase 3 safety population was then queried for adverse events related to embolic phenomena, occurring at any point during the study (Table 30).

Table 30: TEAEs Potentially Related to Infusion of Particulate Drug Material at Any Point During the Phase 3Trials

	9766-CL-0103		9766-CL-0104			
	Isavuconazonium (N = 146)		Isavuconazonium (N = 257)		Voriconazole (N = 259)	
AE	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**
Pulmonary Embolism (PT)	1	0.7%	0	0	3	1.2%
Embolic and Thrombotic Events (nSMQ)	12	8.2%	9	3.5%	17	6.7%
Pulmonary Hypertension (nSMQ)	0	0	0	0	2	0.8%
Endocarditis (PT)	0	0	1	0.39%	0	0
Infusion Site Reactions (HLT)	3	2.1%	7	2.7%	2	0.8%

PT: Patient level term; nSMQ: Narrow standardized medical query; HLT: High level term
Source: Reviewer generated using datasets from studies 9766-CL-0103 and 9766-CL-0104

Overall, there were more embolic and thrombotic events associated with voriconazole use as compared to isavuconazonium. Treatment emergent infusion site reactions associated with isavuconazonium and voriconazole are discussed in section 9.8.2. None of the reactions were considered serious, and all resolved.

9.7.3 QT Segment Shortening

Two Thorough QT studies were conducted, neither of which showed QT prolongation, and both showed QT shortening. For the isavuconazonium 200 mg and 600 mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 msec and by 19 to 25 msec, respectively, within 1 hour and 24 hours post dose. No QTcF < 330 msec was observed. No QTcF prolongation was observed in the isavuconazonium treatment groups.

The frequency of QT shortening TEAEs among isavuconazonium-treated patients in the phase 3 controlled trial was 0.4% (one patient) compared to none in the voriconazole treatment group. This was the only short QT adverse event in the integrated safety database.

> Study subject 004-5202-01, a 39 year-old female with a history significant for hyponatremia, hypochloremia, hypomagnesemia, and hypokalemia received ISA for 10 days. Her baseline QTcF was 394 msec. On Day 2, ECG showed sinus tachycardia (HR 135 bpm), QT 275 msec, and QTcF 360 msec. On Day 8, patient experienced non-serious TEAEs of abnormal T wave and QT shortened (QT 301 msec; HR 119 bpm; QTcF 378 msec). On Day 10, QT was 287 msec, HR 109 bpm, and QTcF 351 msec. The investigator assessed the TEAEs as possibly related to ISA. No treatment was administered. TEAE of QT shortened was reported as resolved on Day 9; TEAE of abnormal T wave was ongoing. The patient withdrew consent and was discontinued from the study on Day 10.

In Table 31 below, absolute values and changes from baseline for QTcF based on post-baseline extreme values in the Phase 3 Controlled Study are summarized. Five isavuconazonium-treated patients (2.0%) experienced post-baseline QTcF < 330 msec. In all of these patients, QTcF < 330 msec was a single, transient finding. None were associated with ventricular arrhythmias.

Table 31: QTcF Interval: Number and percentage of patients meeting threshold criteria and decreases from baseline (post baseline): Phase 3 Controlled Trial

QTcF Category	Isavuconazonium (N = 257)	Voriconazole (N = 259)
N‡	250	252
< 360 msec	51 (20.4%)	41 (16.3%)
< 330 msec	5 (2.0%)	5 (2.0%)
< 300 msec	1 (0.4%)	0
N‡	227	224
Decrease > 30 msec	73 (32.2%)	68 (30.4%)
Decrease > 60 msec	17 (7.5%)	10 (4.5%)

Post baseline: Includes all post-baseline measurements up to 10 days following last dose of study medication.

‡Number of patients with both baseline and at least one post-baseline value within 10 days after last dose of study drug.

Percentages are calculated as the total number of patients within the maximum value category divided by the total number of patients with a non-missing value.

Source: Modified from 9766-CL-0104 Clinical Study Report, End-of-Text Tables 12.6.4 3 and 12.6.4.4.

Short QT syndrome (SQTS) is a rare genetic condition, defined as a QT interval < 320 msec[14]. SQTS diagnostic criteria including QTc (QT interval corrected for heart rate), clinical history, family history, and genotype were developed based on a systematic review of SQTS cases reported in the literature. These criteria specify QTc < 330 msec, in the absence of other risk factors, as being associated with an intermediate probability of SQTS[15]. While familial QT shortening is a well-described clinical syndrome that can result in severe life-threatening ventricular arrhythmias, there is no consensus in the scientific literature regarding thresholds of concern for drug induced QT shortening[16]. Drug induced QT shortening due to isavuconazonium therefore presents a risk in patients with familial short QT syndrome, but it is difficult to estimate risk for the general patient population.

[14] Webster G, Berul CI, An update on channelopathies from mechanisms to management. *Circulation*. 2013;127(1):126-40.

[15] Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol*. 2011;57(7):802-12.

[16] Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. *Br J Pharmacol*. Jan 2010; 159(1): 58–69.

9.8 Drug Class Associated Adverse Events of Interest

9.8.1 Hypersensitivity Reactions

Potential anaphylaxis and severe cutaneous reactions (SCAR) were reported in the same proportion of isavuconazonium- (1.9%) and voriconazole-treated (1.9%) patients, and are summarized in Table 32 below. There were no events of anaphylaxis or severe cutaneous adverse reactions in the Phase 1 or Phase 2 integrated safety populations.

Table 32: Treatment Emergent Anaphylaxis/SCAR in the Phase 3 Controlled Population

MedDRA v12.1	Isavuconazonium	Voriconazole
Overall	5 (1.9%)	5 (1.9%)
Anaphylactic reaction	0	2 (0.8%)
Anaphylactic shock	1 (0.4%)	0
Circulatory collapse	1 (0.4%)	0
Dermatitis exfoliative	1 (0.4%)	1 (0.4%)
Erythema multiforme	2 (0.8%)	0
Shock	0	1 (0.4%)
Toxic skin eruption	0	1 (0.4%)

Source: Reviewer generated using datasets from study 9766-CL-0104

The patient (Subject 3203-04) who experienced anaphylactic shock in the isavuconazonium treatment arm had the reaction during an infusion of human immunoglobulin. Therapy was instituted with methylprednisolone, and treatment with isavuconazonium was not interrupted.

The AE of circulatory collapse (Subject 4910-14) occurred and resolved on Day 39 in a patient with history of tachyarrhythmias, and cardiac failure, while on oral therapy. No specifics regarding the circulatory collapse were provided. Vital sign measurements reported on Day 40 included blood pressure of 140/70 mm Hg, pulse rate of 88 bpm and an oral equivalent temperature of 36.6°C. The investigator reported the results from an ECG performed on Day 40 as abnormal but not clinically significant with a “minimal P value prolongation”. The patient refused further study drug treatment beyond Day 39. On Day 80, the patient experienced cardiac decompensation, which was reported as an SAE of cardiac failure; the patient died that same day.

The AE of exfoliative dermatitis occurred in a patient (Subject 3304-05) with a history of toxiderma on Day 109, 15 days after the last dose of study medication.

There were two cases of erythema multiforme. The first, (Subject 4910-15) had episodes of erythema on Days 9, 31 and 32. The event of interest occurred on Day 31, 10 days after the last dose of study medication.

The second (Subject 3206-01) had erythema reported subsequent to an AE of vasculitis affecting torso, back, arms and legs from study Day 31 to 115. The patient completed 84 days of treatment with isavuconazonium.

There were, however, instances of AEs recorded as infusion reactions that could be considered hypersensitivity reactions:

1) Subject 004-4910-21 experienced a SAE listed as dyspnea that occurred during infusion. The patient improved with both diuresis and steroids. The study drug,

isavuconazonium, was stopped and not reinstated. It is reasonable to consider anaphylaxis as a possible etiology of the SAE.

2) Subject 004-9703-08 discontinued IV isavuconazonium on study Day 2 due to an AE of "allergic dermatitis", treated with steroids. The investigator considered the reaction probably related to isavuconazonium infusion.

3) Patient 004-5604-01 discontinued isavuconazonium due to severe chills/rigors on infusion Day 11. The adverse reactions recurred on re-challenge the next day. Vital signs were unremarkable. Isavuconazonium was permanently discontinued.

The cases of anaphylaxis identified within the phase 3 controlled isavuconazonium-treated population are confounded by underlying medical conditions, and concurrent medications. In the healthy phase 1 population there were no reported instances of anaphylactic or cutaneous reactions. The three cases outlined above, while not definitive, do suggest the potential for hypersensitivity reactions with isavuconazonium by temporal association and resolution following de-challenge.

9.8.2 Infusion-Related Reactions

Infusion-related reactions are defined as serious adverse reactions that occur during or within two days following IV dosing. The overall frequency of potential infusion-related serious TEAEs occurring within two days after IV dosing among isavuconazonium-treated patients in the phase 3 controlled trial was 10.1% compared to 6.9% in the voriconazole treatment group. All patients in this trial were included in this analysis as all received at least one IV dose of study drug.

In Table 33, all infusion-related TEAE resulting in discontinuation in the phase 2 and 3 combined safety populations are summarized. In the phase 1 healthy subject population, there were no infusion-related serious TEAEs or TEAEs that led to study drug discontinuation.

Table 33: Infusion-related TEAEs that led to study drug discontinuation: Phase 2 and 3 Population

MedDRA v12.1 Preferred Term	Phase 2 & 3 Isavuconazonium (n = 380)	Phase 3 Isavuconazonium (n = 259)
Overall	11 (2.9%)	8 (2.2%)
Acute respiratory failure	1 (0.3%)	1 (0.3%)
Chills	1 (0.3%)	1 (0.3%)
Convulsion	2 (0.5%)	2 (0.6%)
Dyspnea	2 (0.5%)	2 (0.6%)
Epilepsy	1 (0.3%)	1 (0.3%)
Hypersensitivity	2 (0.5%)	0
Hypotension	1 (0.3%)	1 (0.3%)
Infusion Reaction	1 (0.3%)	0
Respiratory failure	2 (0.5%)	2 (0.6%)

Source: Modified from Applicant "Isavuconazole Risk Management Plan", Table 32

Several cases are consistent with infusion related reactions, which are known to occur with a variety of intravenously administered agents, including antifungal agents such as amphotericin B and voriconazole[17].

[17] Walsh, T.J. *et al.* "Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever." N Engl J Med. 2002 Jan 24;346(4):225-34.

10 POINTS FOR ADVISORY COMMITTEE DISCUSSION

1. Has the applicant provided substantial evidence of the safety and effectiveness of isavuconazonium for the treatment of invasive aspergillosis?

    - If yes, please provide any recommendations concerning labeling.
    - If no, what additional studies/analyses are needed?

2. Has the applicant provided substantial evidence of the safety and effectiveness of isavuconazonium for the treatment of invasive mucormycosis?

    - If yes, please provide any recommendations concerning labeling.
    - If no, what additional studies/analyses are needed?